The American Journal of Medicine



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The American Journal of Medicine

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Systemic Lupus Erythematosus—Disease of an Unusual Immunologic Responsiveness?
HALSTED R. HOLMAN 525

Clinical Studies

Studies on Respiratory Mechanics and the Work of Breathing in Pulmonary Fibrosis
JOHN R. WEST AND JAMES K. ALEXANDER 529

This detailed study of nine patients with pulmonary fibrosis provides additional confirmation of the reduction in pulmonary compliance, i.e., increased rigidity of the lung, in this disorder. Painstaking analysis showed good correlation between the reduction in pulmonary compliance and decrease in total lung volume but not with arterial blood oxygen values. This would suggest that the fibrotic alterations responsible for reduction in compliance involve areas not related to diffusion of gases in the lung.

Pulmonary Ventilation. Blood Flow Relationships in Interstitial Disease of the Lungs
JOHN READ AND R. S. WILLIAMS 545

By using a mass spectrometer, it was possible to make single breath analyses of argon, carbon dioxide and oxygen concentrations, and such sensitive measurements revealed hitherto undetected impairment in the distribution of inspired air in patients with "pure" interstitial disease of the lungs. In the presence of uniform blood flow, such uneven ventilation leads to marked ventilation-perfusion imbalance. It is implied that the disturbances disclosed by these sensitive methods have clinical significance.

The Respiratory Effects of Progesterone in Severe Pulmonary Emphysema
JAMES H. CULLEN, VICTOR C. BRUM AND WILLIAM U. REIDT 551

Hypercapnia in syndromes of alveolar hypoventilation remains a challenge despite use of bronchodilators and various mechanical aids to ventilation. It is of considerable importance to evaluate newer agents which affect CO_2 levels in arterial blood. The authors report the effect of progesterone in seven patients with emphysema. They confirm the increase in total and alveolar ventilation, but observed it to be smaller than previously reported. Effective reduction in CO_2 levels was achieved in three cases. The mechanism of action remains obscure, but no bronchodilator effect was demonstrated.

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new for total management of itching,[1,2] inflamed,[3,4] infected[5,6] skin lesions



Dermatitis repens [with staph and monilia] 7 weeks duration

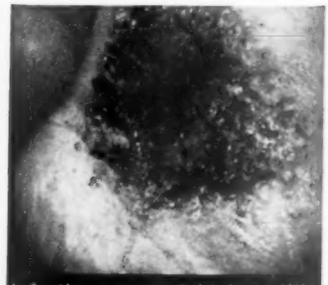


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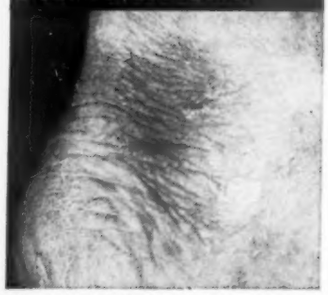
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Infectious eczematoid dermatitis of ankle—5 years duration



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References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H.: Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith J.G., Jr.; Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.

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The Oxyhemoglobin Dissociation Curve in the Common Hemoglobinopathies
THEODORE RODMAN, HENRY P. CLOSE, RICHARD CATHCART AND MAY K. PURCELL 558

Arterial unsaturation occurs in some hemoglobinopathies, notably pure S and C-S hemoglobinopathies, because of a displacement to the right of the *in vivo* oxyhemoglobin dissociation curve. The reason for this displacement is not altogether clear but, it is suggested, may be related to reduction in the intracellular pH of the red cell. Whatever the mechanism, the point of particular clinical interest is that arterial unsaturation in sickle cell anemia and C-S hemoglobin disease need not be ascribed to pulmonary insufficiency resulting from multiple pulmonary thromboses or related causes.

The Paradox of the Antibody Response to Streptodornase. The Usefulness of Anti-desoxyribonuclease B as an Indication of Streptococcal Infection in Patients with Acute Rheumatic Fever . . . . . LEWIS W. WANNAMAKER 567

Although group A streptococci almost invariably produce large amounts of desoxyribonuclease, neutralizing antibody has been found only sporadically in the blood after streptococcal infection. The present study explains this paradox by describing three serologically distinct desoxyribonucleases, designated streptococcal Dnases A, B and C. Only antibody to Dnase B occurs regularly in high titer after streptococcal infection, so regularly indeed that it can be made the basis for a test for rheumatic fever. The anti-Dnase B test may be positive in some cases with only questionably elevated antistreptolysin O titers, and appears to have distinct advantages over the antihyaluronidase and antistreptokinase tests.

Disturbances of Digestive Physiology Following Acute Drinking Episodes in "Skid-Row" Alcoholics MELVIN SMALL, AMILCAR LONGARINI AND NORMAN ZAMCHECK 575

What has for years been designated acute "alcoholic gastritis" is here subjected to more precise analysis in a large number of "skid-row" alcoholics studied at the end of a long spree. Considering the substantial insult, this investigation, like previous studies, reveals remarkably few indications of serious damage to the gastrointestinal tract, liver or pancreas, although minor abnormalities were common enough. In many cases there was evidence of reduction in gastric acid production, fatty liver, deficits of gallbladder and pancreatic function, and impairment of intestinal absorption. These minor abnormalities may, of course, presage more serious subsequent disease, notably cirrhosis of the liver which (as in most such studies) was rarely present.

The Syndrome of Congenital Goiter with Butanol-Insoluble Serum Iodine
LESLIE J. DEGROOT AND JOHN B. STANBURY 586

The authors cite in some detail five cases illustrative of one of several distinct inborn errors of metabolism responsible for sporadic congenital cretinism with goiter. The cases described are distinguished by the presence in the serum (and sometimes in the urine) of an iodinated polypeptide or protein which is incompletely extractable from acidified serum by n-butanol. It is not yet clear whether the compound in question is a normal or abnormal intermediate in the biosynthesis of thyroglobulin. In any event, presumably as the result of innate deficiency of a necessary synthesizing enzyme, thyroglobulin is insufficiently elaborated, and hypothyroidism results. The clinical symptoms and signs respond to administration of desiccated thyroid, which should be instituted early in life to prevent permanent physical and mental retardation.

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Review

The Serum Proteins in Health and Disease. Filter Paper Electrophoresis
M. A. OGRYZLO, MARGARET MACLACHLAN, J. A. DAUPHINEE AND A. A. FLETCHER 596

The authors summarize a large experience with filter paper electrophoresis of serum and urinary proteins, employing specially designed electronic scanning, integrating and recording devices. The results are in general accord with those reported by others but bring out a number of interesting points not previously emphasized sufficiently. These bear on the general incidence of specific abnormal serum proteins including cryoglobulins; the association of hypogammaglobulinemia with a variety of malignant disorders; apparent differences in the protein patterns in the nephrotic syndrome of glomerulonephritis and that associated with systemic lupus erythematosus; and other findings of clinical interest.

Seminar on Mycotic Infections

The Use of Amphotericin B in the Treatment of Coccidioidal Disease
WILLIAM A. WINN 617

Amphotericin B, administered by appropriate routes and in the required dosage, has proved to be the most effective therapeutic agent for coccidioidal disease yet discovered. Dr. Winn offers documentation of this claim by citing nine patients with impending or demonstrated disseminated infection, six patients with coccidioidal meningitis, and seven patients with a variety of sites of infection including skin abscesses. The problems of administration over the long periods necessary are not simple, however, and the small details required for successful management are therefore (properly) emphasized.

Clinicopathologic Conference

Hemiparesis, Coma and Uremia 636

Clinicopathologic Conference (Washington University School of Medicine).

Case Reports

Hemoglobin S-C Disease with Fat Embolism. Report of a Patient Dying in Crisis; Autopsy Findings
WILLIAM B. OBER, MICHAEL S. BRUNO, RAYMOND M. SIMON AND LEO WEINER 647

An instructive case and discussion.

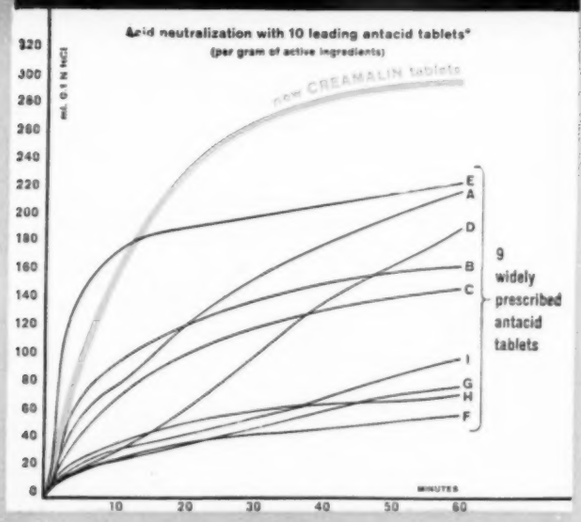
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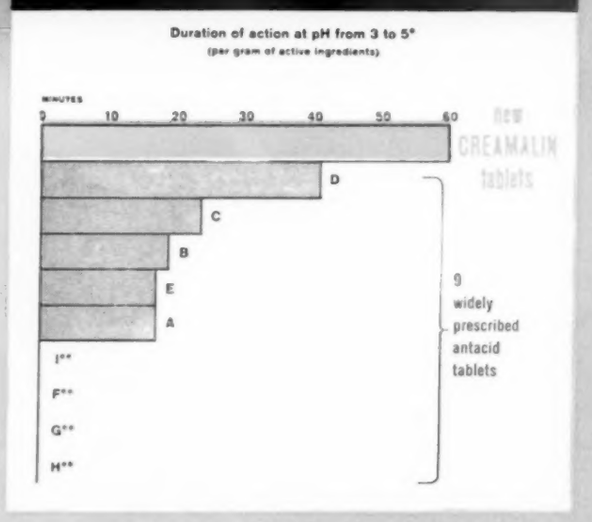
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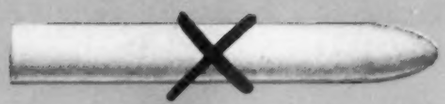
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*Hinkel, E. T., Jr., Fisher, and Tainter, M. L.: A new highly reactive aluminum hydroxide complex for gastric hyperacidity. To be published.
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VOLUME TWENTY-SEVEN NUMBER FOUR

Electrocardiographic and Radiographic Findings in Acute Arsenic Poisoning
ARISTIDES G. GOUSIOS AND LESTER ADELSON 659

Arsenic poisoning, a not infrequent medicolegal problem, may escape clinical recognition. This case report illustrates many of the typical features of acute arsenic poisoning and presents some electrocardiographic findings of interest. Pathologic and toxicologic analyses are described.

Renal Tubular Acidosis and Potassium Loss
BURTON A. LERNER AND PHILIP W. BRICKNER 664

An interesting case.

Malabsorption Syndrome Associated with Metastatic Carcinoid Tumor
O. DHODANAND KOWLESSAR, DAVID H. LAW AND MARVIN H. SLEISENGER 673

The point made deserves notice, that excessive circulating 5-hydroxytryptamine in patients with metastatic carcinoid tumor may in some instances cause malabsorption and steatorrhea sufficient to contribute to weight loss and other manifestations of debilitation.

"Stiff-Man" Syndrome
ROBERT E. WHALEN, JOSEPH J. COMBS, JR. AND WILLIAM P. DEISS, JR. 678

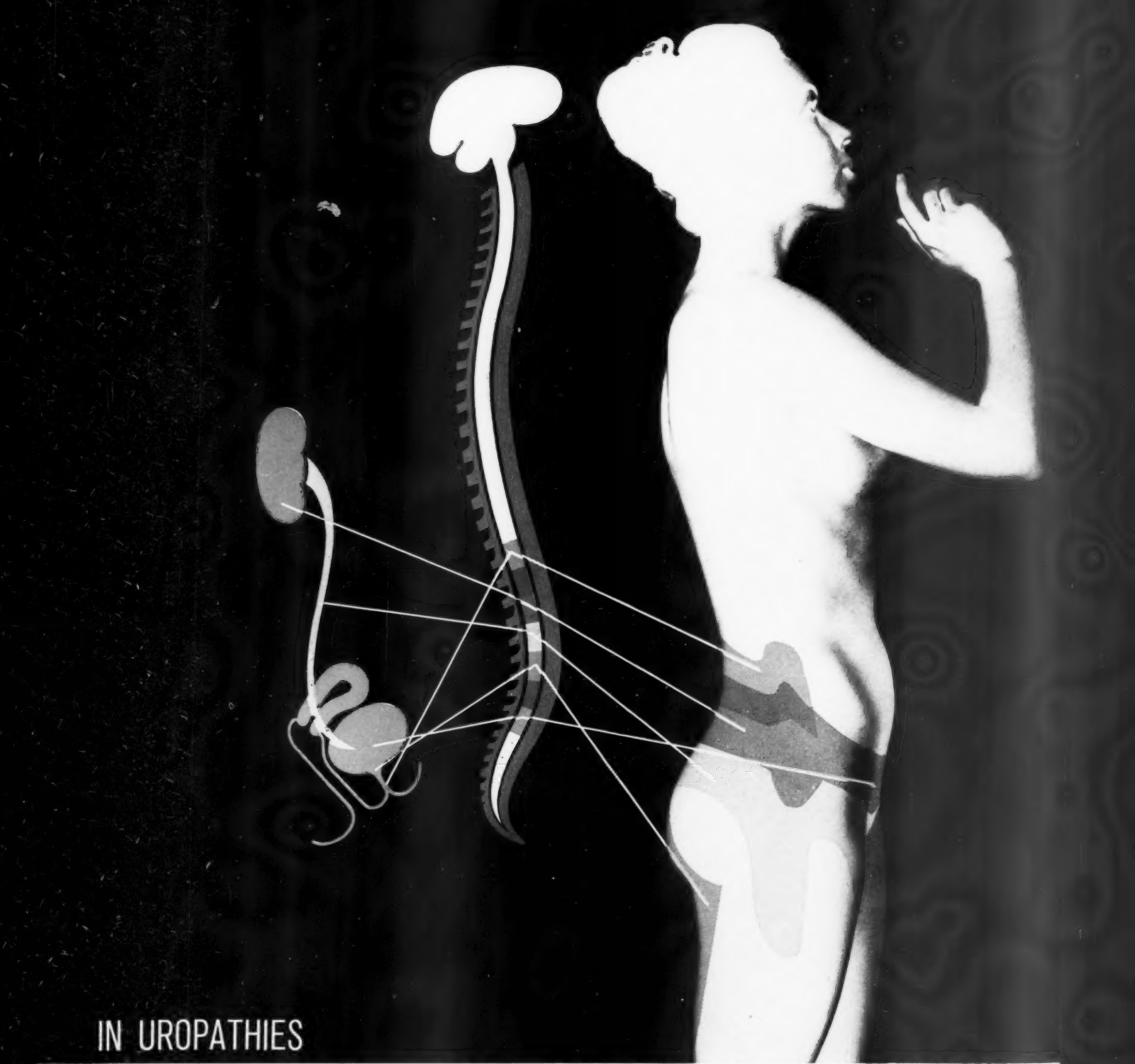
A well studied case of progressive muscular rigidity, a rare syndrome which has been receiving increasing attention. Persistent leukopenia (hitherto undescribed) was noted. Glycosuria, previously reported by others, was also noted. It is suggested but not established that the disorder may be due to a metabolic defect.

Hereditary Ectodermal Dysplasia of the Anhidrotic Type Associated with Primary Hypogonadism . . . . . DANIEL N. MOHLER 682

An interesting account of two examples of this unusual anomaly.

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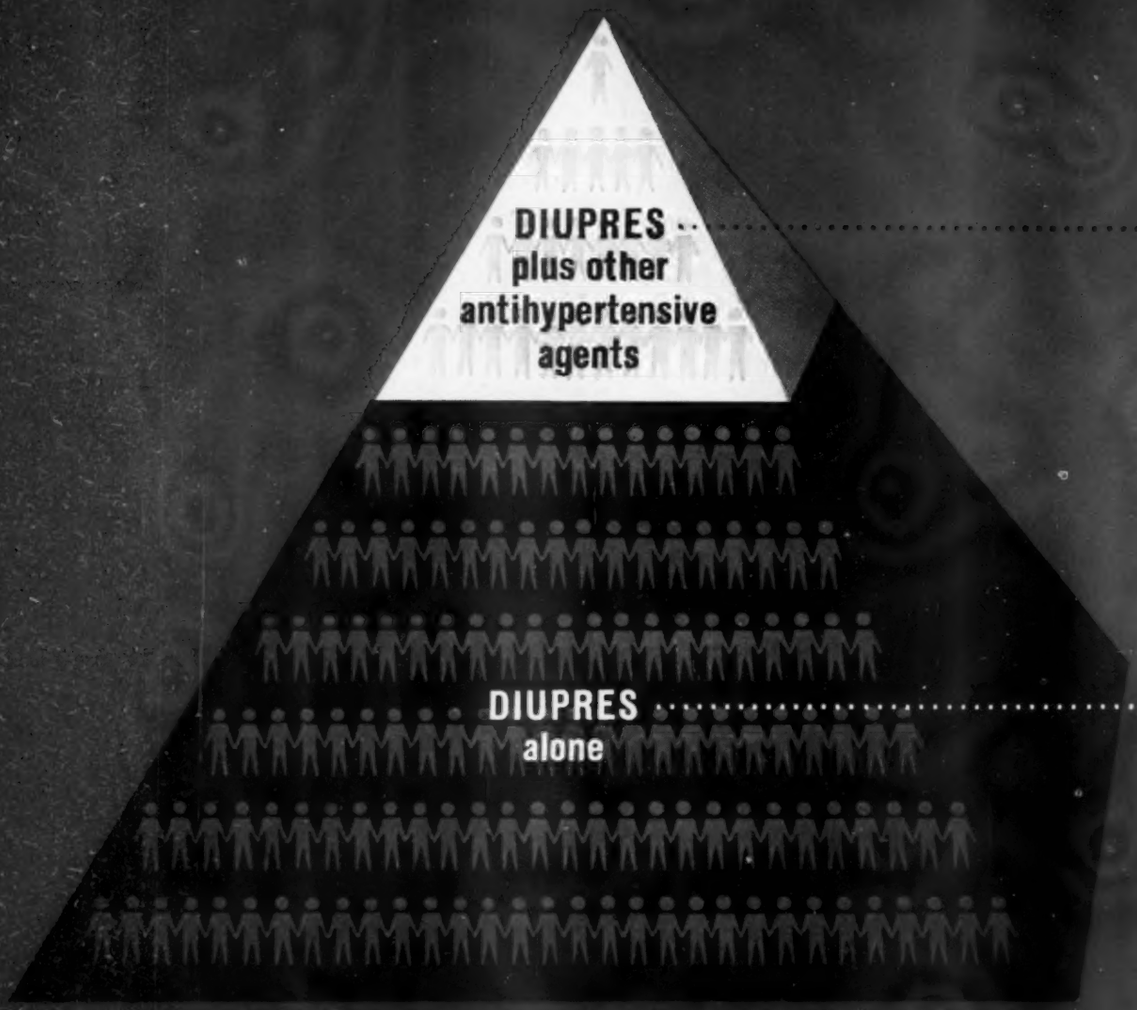
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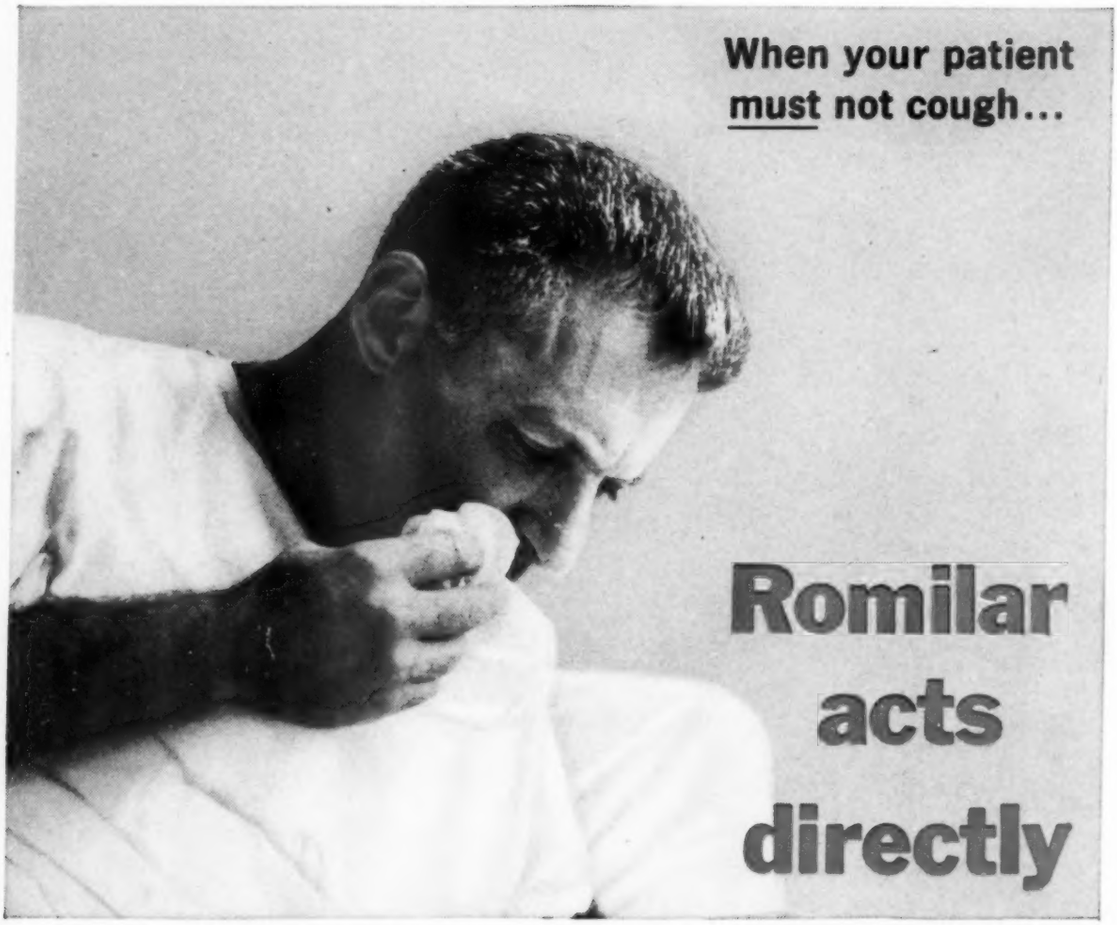
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ROMILAR, the non-narcotic cough specific, has one pharmacologic action — cough suppression. There is no central depressant or analgesic effect; and there is no tolerance liability, no addictive potential.[2-9]

Bibliography: (1) N. Ralph, Am. J. M. Sc. 227:297, 1954. (2) H. A. Bickerman, in W. Modell, Ed., Drugs of Choice 1958-1959, St. Louis, The C. V. Mosby Company, p. 557. (3) H. A. Bickerman, E. German, B. M. Cohen and S. Itkin, Am. J. M. Sc. 234:191, 1957. (4) L. J. Cass, W. S. Frederik and J. B. Andosca, Am. J. M. Sc. 227:291, 1954. (5) L. J. Cass and W. S. Frederik, J. Lab. & Clin. Med. 48:879, 1956. (6) L. J. Cass and W. S. Frederik, New England J. Med. 249:132, 1953. (7) H. Isbell and H. F. Frazer, J. Pharmacol. & Exper. Therap. 107:524, 1953. (8) W. M. Benson, P. L. Stefko and L. O. Randall, J. Pharmacol. & Exper. Therap. 109:189, 1953. (9) New and Nonofficial Drugs 1959, Philadelphia, J. B. Lippincott Company, p. 326.

SUPPLY:
ROMILAR Syrup in bottles of 4 oz, 16 oz and 1 gal.
ROMILAR Tablets in bottles of 20, 100 and 500.

Romilar® Hydrobromide — brand of dextromethorphan hydrobromide.

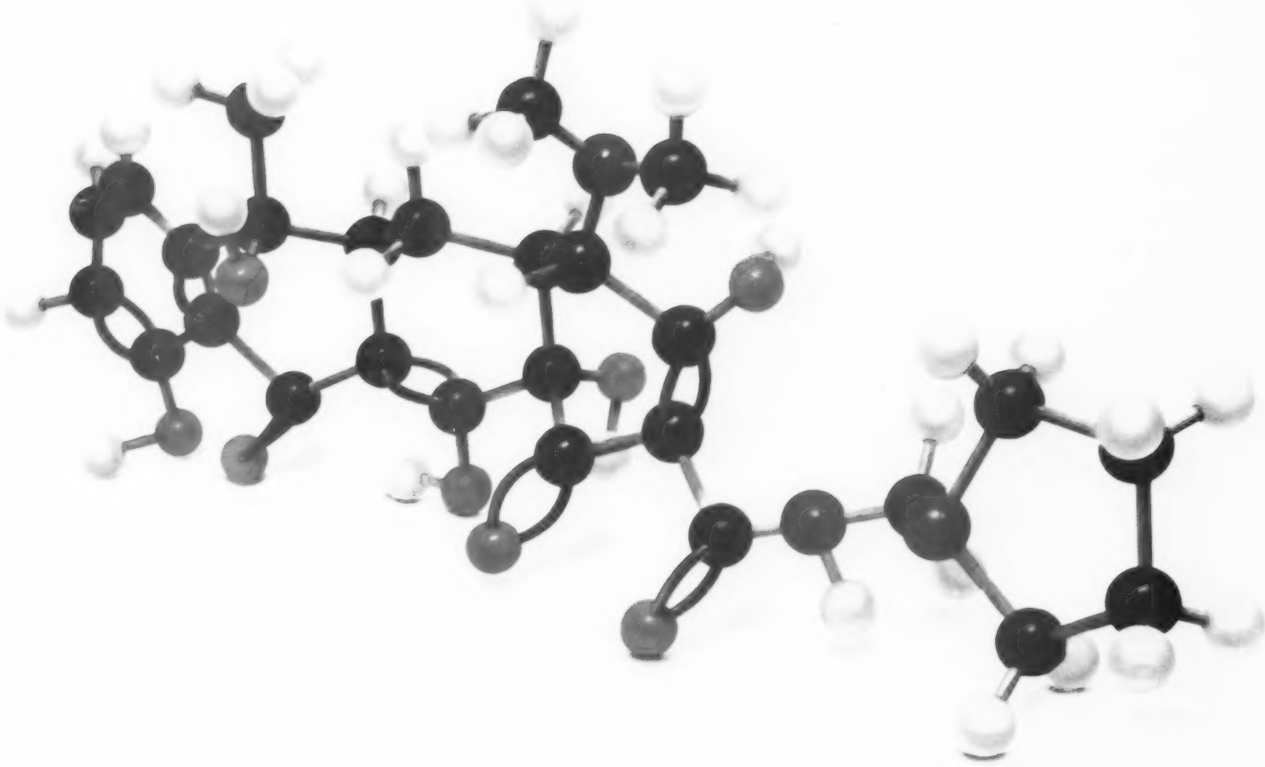
Romilar

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, N. J.

Bristol Laboratories
announces
the synthesis of an **improved**
broad-spectrum antibiotic

SYNTETRIN™

N—(PYRROLIDINOMETHYL) TETRACYCLINE



a new molecule

a new synthetic derivative of tetracycline with new attributes of significant value in therapy

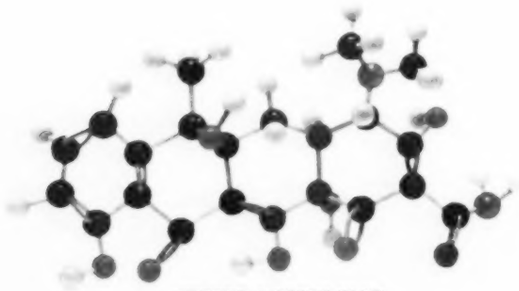
SYNTETRIN

SYNTETRIN is N—(pyrrolidinomethyl) tetracycline, a new derivative of tetracycline developed by Bristol Laboratories. It is highly soluble over the entire physiological pH range (2,500 times more soluble than tetracycline – see Figure 1).

SYNTETRIN is a *different* molecule, as can be seen by examining the chemical structure and the molecular weights of both tetracycline and SYNTETRIN.

A pyrrolidinomethyl group replaces one of the hydrogen atoms in the NH_2 group as shown at the extreme right of the molecule.

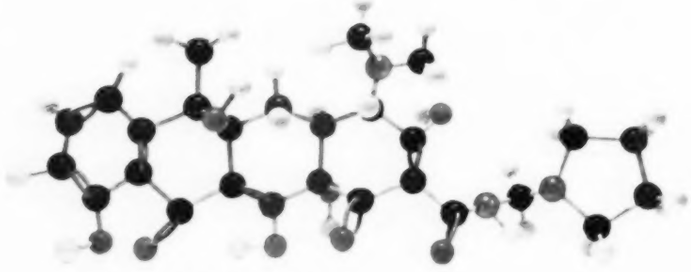
The important point is that there is a change in the *basic molecular structure* of tetracycline. The new properties of SYNTETRIN do not derive from salt or complex formation, or from adjuvant action.



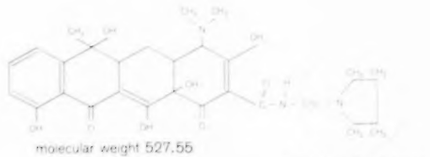
TETRACYCLINE



molecular weight 444.45



SYNTETRIN



molecular weight 527.55

pyrrolidinomethyl group

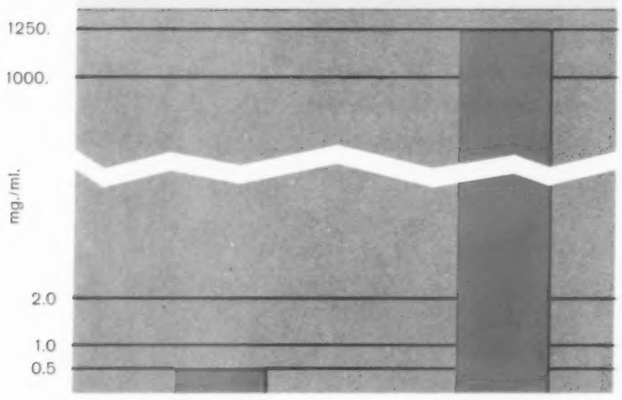
SYNTETRIN *is at present available only in intramuscular and intravenous formulations.*

greater 24-hour therapeutic activity with Syntetrin **I. M.**

Total antibiotic activity with SYNTETRIN I.M. is more than twice that with tetracycline phosphate complex I.M. over a 24-hour period. This is evident from a crossover study of blood levels of 15 subjects by Kligman.[1] His plotted data, shown in Figure 2, indicate that the area under the curve of SYNTETRIN blood levels is more than twice that of tetracycline phosphate complex. With the area under the curve of tetracycline phosphate complex considered as 100, the area under SYNTETRIN was measured with the planimeter as 204. The probability of this difference occurring by chance is less than 1 in 1,000. It is important to note that both products contained the labeled quantity of active ingredient equivalent to 250 mg. of tetracycline HCl activity, and each product contained a 10 per cent overfill. This enhancement of total antibiotic activity seems to be related to the unique solubility of SYNTETRIN and its more efficient absorption from intramuscular sites.

FIGURE 1

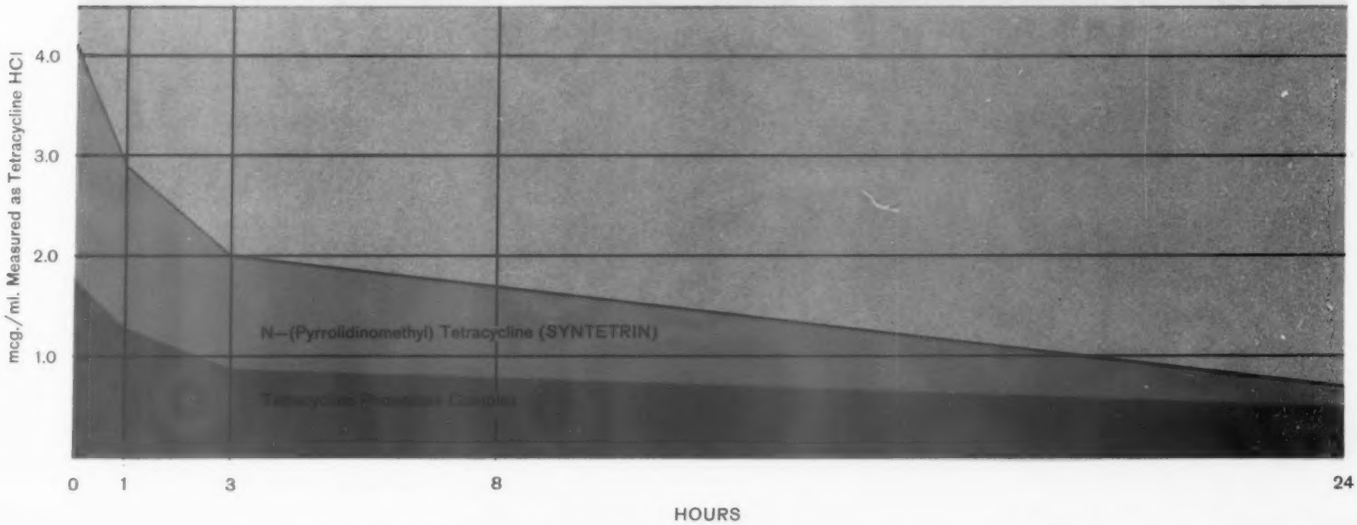
Solubility in water



Adapted from Siedel, W., Soder, A., and Lindner, F.: Munchen. med. Wchnschr. 100:661, 1958.

FIGURE 2

Crossover Study of Tetracycline Serum Concentration in the Same 15 Human Subjects Following Intramuscular Injection of 350 mg. SYNTETRIN or 320 mg. Tetracycline Phosphate Complex. Each Injection Equivalent to 250 mg. Tetracycline Hydrochloride Activity



The differences between SYNTETRIN and tetracycline levels at all hours shown above are statistically significant. (This difference would occur by chance in less than 1 in 1,000 times.)

with SYNTETRIN effective antibacterial activity even at its lowest blood

TABLE I

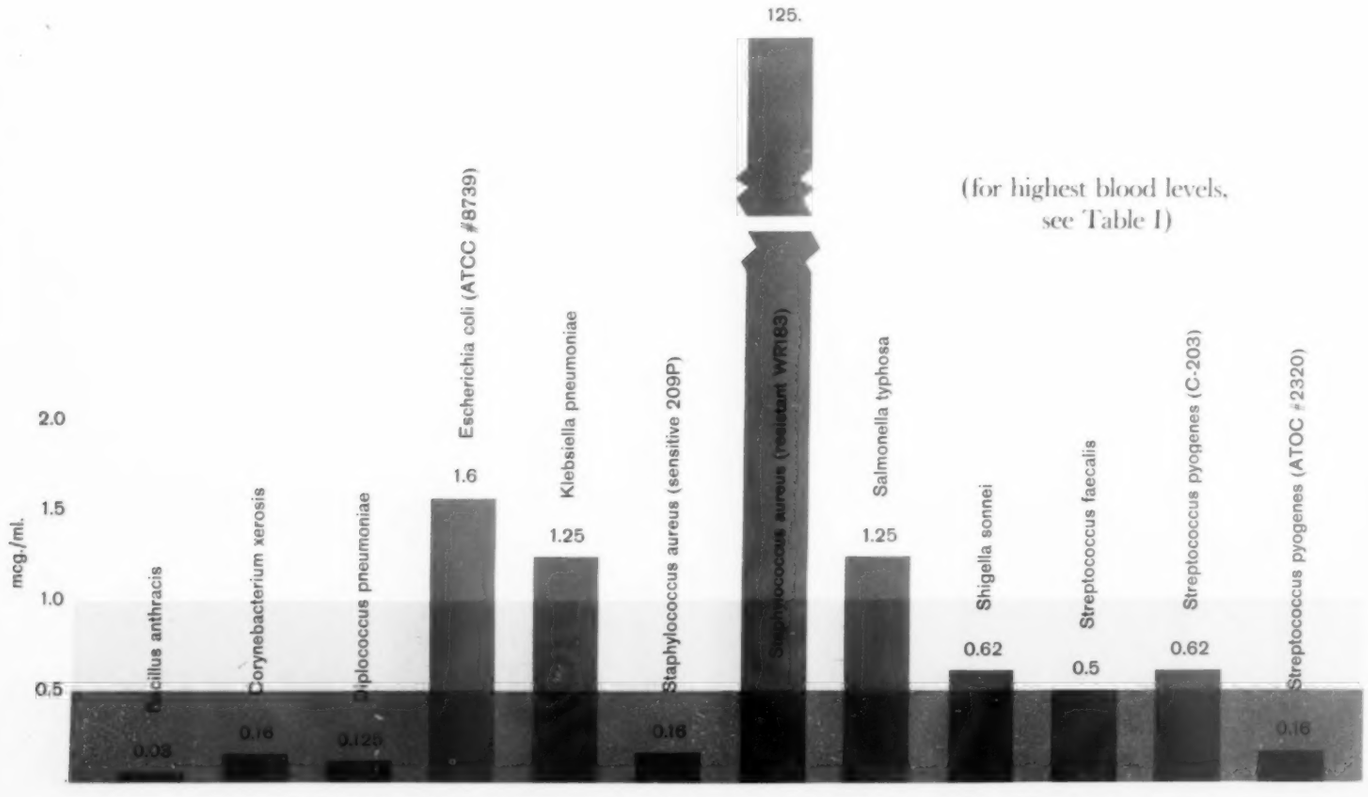
Serum Concentration Studies (mcg./ml. as Tetracycline HCl) of SYNTETRIN in Humans
Unit dose: 350 mg. q. 24 hours I. M.

INVESTIGATOR	NO. OF SUBJECTS	HOURS AFTER ADMINISTRATION							
		1	24	25	48	49	72	73	96
Kligman[1]	5	1.5	0.5	3.5	0.8	4.0	0.9	3.2	1.0
Cohn[2]	9	3.2	0.6	4.2	0.6	4.6			
Cronk[3]	10	5.2	0.6	5.0	0.6	5.2	0.8	5.5	0.8

Note that the lowest blood levels reached before each daily injection, shown by the red figures, indicate either *maintenance* or *increase*. While of less importance than the above, it is significant that the successive blood level peaks generally rose, i.e., at 25, 49, and 73 hours.

FIGURE 3

Minimum In Vitro* Concentrations of SYNTETRIN Which Will Inhibit Growth of Some Pathogens Against Which Tetracyclines Are Ordinarily Used



*two-fold serial tube dilution technique in heart infusion broth; measured as tetracycline HCl

is sustained–
levels–throughout therapy

Figure 3 clearly demonstrates that the minimum in vitro concentrations of SYNTETRIN which will inhibit the organisms are reached in most instances even with the *lowest blood level* attained throughout the period of therapy (note the range of lowest blood levels from Table I indicated by light blue horizontal band).

Also, Table I shows *enhancement* of these levels after repeated injections. Figure 3 indicates that this may be therapeutically significant for some patients, because minimum inhibitory concentrations for certain organisms will be reached with SYNTETRIN on continuing therapy.

The advantages of parenteral administration of Syntetrin in selected patients

There are three categories of patients which will benefit from the parenteral administration of SYNTETRIN:

1. *Patients who require frequent force-feeding or special diets based on milk.* Various investigators have emphasized that food, milk, and calcium may interfere with the absorption of orally administered tetracyclines from the digestive tract.

Price *et al.*[4] made a detailed study in relation to the observed antagonistic effect of milk on oxytetracycline and chlortetracycline.

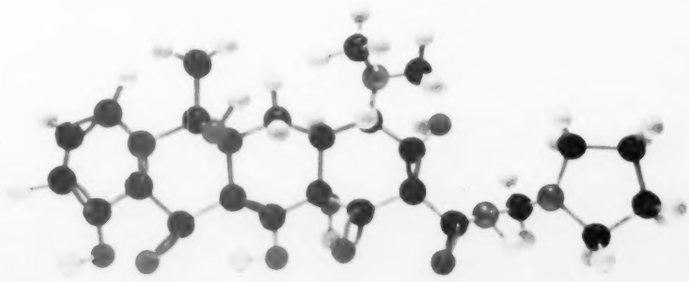
They clearly demonstrated that readily ionizable salts of calcium and magnesium have considerable inhibitory effect on the action of such antibiotics in vitro. Dearborn and associates,[5] in animal experiments, showed that food and dicalcium phosphate distinctly lowered antibiotic activity; and Sweeney and his colleagues[6] demonstrated that calcium compounds decreased the absorption of tetracycline in man.

2. *Patients with diseases causing absorption difficulties.* Finland[7] points out that, in addition to difficulties in absorption associated with G. I. pathology, serious systemic illness may interfere with antibiotic absorption. He states that "marked irregularities in absorption . . . can be expected in the routine use of multiple doses [by the oral route] in sick patients, when large and often excessive doses must be used to insure therapeutic success."

Such difficulties in achieving therapeutic levels, e. g., in pneumonia associated with cardiac insufficiency, may be avoided by the parenteral route.

3. *Patients unable to take anything by mouth.* Examples are patients after G. I. surgery, those requiring gastric intubation, etc.

Indications: SYNTETRIN is recommended for parenteral use for infections caused by tetracycline-sensitive organisms in the above types of patients. While a *single* intramuscular injection of SYNTETRIN is *less painful* than other tetracycline intramuscular preparations, repeated injections of SYNTETRIN may be painful, particularly to children. As soon as the patient's condition suggests that the oral route is dependable, SYNTETRIN I.M. therapy should be changed to TETREX Capsules or Syrup.



SYNTETRIN I.M.

N—(PYRROLIDINOMETHYL) TETRACYCLINE WITH XYLOCAINE®*
FOR INTRAMUSCULAR USE

Supplied in dry-fill vials which must be properly reconstituted before injection. Each single dose vial contains:

SYNTETRIN	350 mg.
Lidocaine	40 mg.
Ascorbic Acid	300 mg.

SYNTETRIN I.M. is also supplied in single dose dry-fill vials containing 150 mg. of SYNTETRIN.

*Xylocaine is the registered trademark of Astra Pharmaceutical Products, Inc. for lidocaine.

also available:

SYNTETRIN I.V.

N—(PYRROLIDINOMETHYL) TETRACYCLINE
FOR INTRAVENOUS USE

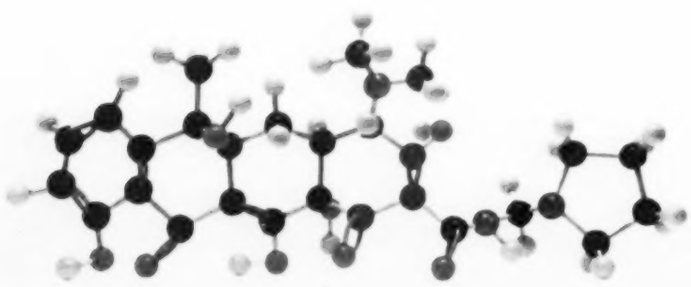
For use only in severe infections when the patient cannot accept oral or intramuscular tetracycline therapy. Each dry-fill vial contains:

SYNTETRIN	700 mg.
Ascorbic Acid	500 mg.

Precautions: SYNTETRIN I.M. should be injected deeply into the upper outer quadrant of the gluteal muscle, using special care to avoid inadvertent injection of the solution into dermal or subcutaneous tissue, resulting in unnecessary pain and tissue reaction. Deep intramuscular injection and avoidance of subcutaneous or dermal spill greatly increase tolerance to the product. The usual precautions for avoidance of extravenous spill should be observed with SYNTETRIN I.V.

References: 1. Kligman, A. M.: Clinical report to Bristol Laboratories Inc. 2. Cohn, I., Jr.: Clinical report to Bristol Laboratories Inc. 3. Cronk, G. A.: Clinical report to Bristol Laboratories Inc. 4. Price, K. E.; Zolli, Z., Jr.; Atkinson, J. C., and Luther, H. G.: Antibiotics & Chemother. 7:672, 1957. 5. Dearborn, E. H. Litchfield, J. T., Jr.; Eisner, H. J.; Corbett, J. J., and Dunnett, C. W.: Antibiotic Med. & Clin. Ther. 4:627, 1957. 6. Sweeney, W. M.; Hardy, S. M.; Dornbush, A. C., and Ruegsegger, J. M.: Antibiotic Med. & Clin. Ther. 4:642, 1957. 7. Finland, M.: Antibiotic Med. & Clin. Ther. 5:359, 1958.

Detailed information on indications, dosage and precautions is contained in the package insert; or, write to Medical Director, Bristol Laboratories Inc., Syracuse, New York.
SYNTETRIN ***is now available at your hospital.***



BRISTOL

In skeletal-muscle disabilities . . .

Curbs spasm, relieves rigidity, and relaxes psychic tension

Of all muscle relaxants in current use, only meprobamate is supported by hundreds of published clinical studies that demonstrate relaxing action on both the brain and the skeletal musculature. EQUANIL reduces muscular spasm and tension, aids in the restoration of mobility, speeds rehabilitation, lessens the emotional overlay.

Prescribe it in spasm or tension secondary to: sprains, strains, contractures, fibrositis, myositis, low-back syndrome, frozen shoulder, cervical-rib syndrome, herniated intervertebral disk, wryneck, rheumatoid arthritis, rheumatoid or traumatic spondylitis, certain neuromuscular disorders.

Equanil

Meprobamate, Wyeth

Wyeth Philadelphia 1, Pa.



NEW concept

in chronic constipation . . .

and especially that associated with
the irritable bowel syndrome



DECHOTYL

TRABLETS*

provides physiologic support until function returns

*T.M. for AMES trapezoid-shaped tablet.



DECHOTYL™

TRABLETS*

safe, gentle transition to normal bowel function

DECHOTYL provides gentle stimulation of the bowel and helps restore normal consistency of the intestinal contents to gradually re-establish normal bowel function in your chronically constipated patients.

THE RATIONALE of DECHOTYL is based on an effective combination of therapeutic agents:

DECHOLIN®, dehydrocholic acid, AMES, (200 mg.), the most potent hydrocholeretic available, is a chemically pure bile acid and has been used effectively in the treatment of biliary tract disorders for many years. It produces an increased flow of thin bile which helps to lower surface tension of intestinal fluids, promotes emulsification and absorption of fats and mildly stimulates intestinal peristalsis.

Desoxycholic Acid (50 mg.)—a choleretic, also is a chemically pure bile acid and stimulates an increased flow of bile, lowers surface tension and stimulates peristalsis. By emulsifying fat globules, desoxycholic acid aids the digestive action of the fat-splitting enzyme, lipase. DECHOLIN and desoxycholic acid thus favorably influence the constitution and the movement of the intestinal contents.

Dioctyl Sodium Sulfosuccinate (50 mg.) is a wetting agent which lowers surface tension and aids the penetration of intestinal fluids into the fecal mass, providing a moist stool of normal consistency.

EFFECTIVE: Bile influences the constitution as well as the movement of the intestinal contents. The ingredients of major importance are DECHOLIN and desoxycholic acid which increase the flow of bile, lower surface tension, promote emulsification and absorption of fats and mildly stimulate intestinal peristalsis. With dioctyl sodium sulfosuccinate, a good therapeutic effect can be obtained without the danger of toxicity or decreasing effectiveness even when used regularly.

SAFE: Clinical evidence indicates that the constituents of DECHOTYL cause no systemic sensitivity, drug accumulation, habituation or interference with nutrition. Orally, in therapeutic amounts, DECHOTYL is without significant toxic effect. The only side effect following oral administration is diarrhea if the dosage is excessive.

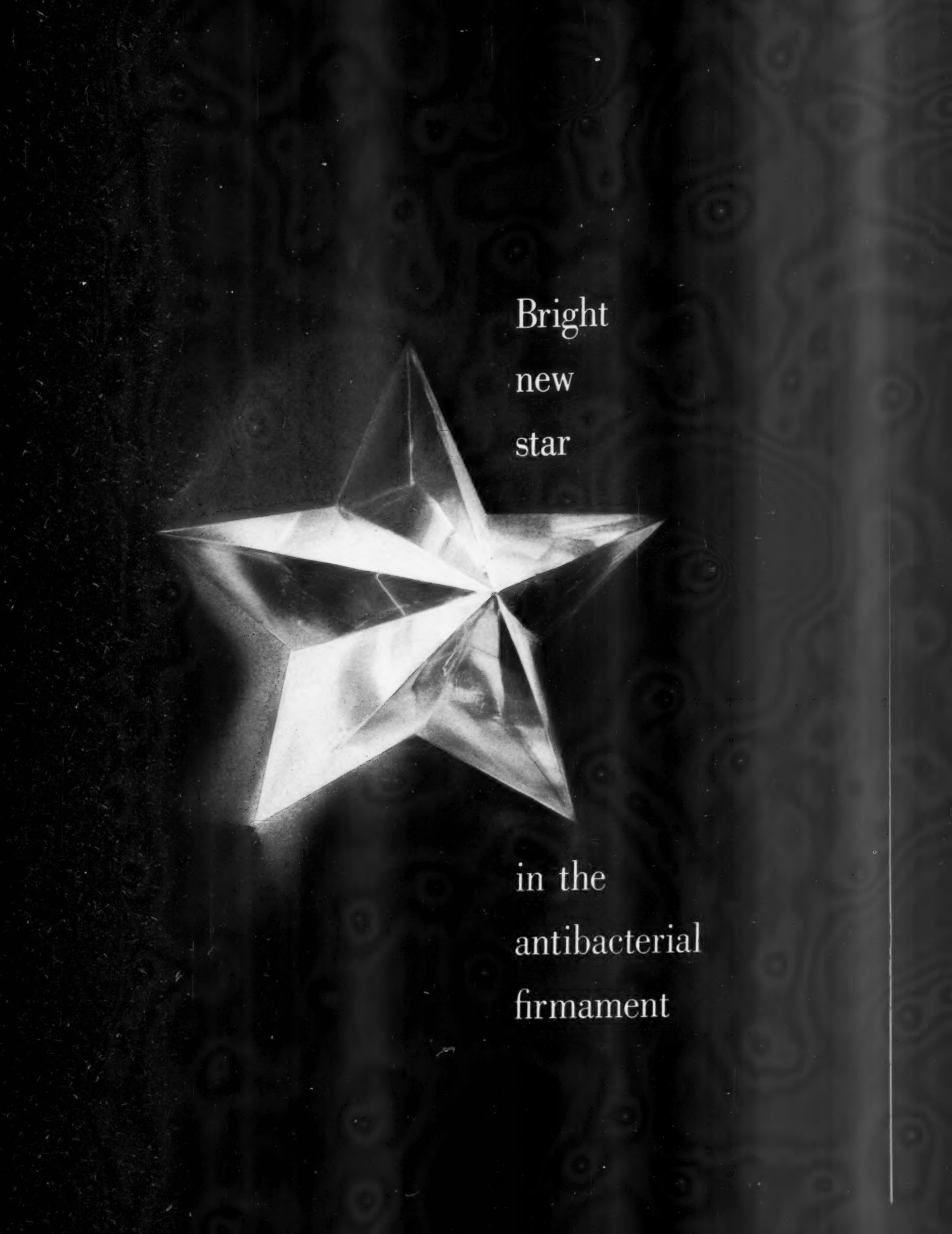
Dosage: *Average adult dose*—TWO TRABLETS* at bedtime. Some individuals initially may require 1 to 2 TRABLETS three or four times daily. *Contraindications:* Biliary tract obstruction; acute hepatitis.

Available: TRABLETS,* coated, yellow, trapezoid-shaped; bottles of 100.

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Bright
new
star
in the
antibacterial
firmament

the first nitrofuran effective orally in systemic bacterial infections

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Effective clinically in upper respiratory infections, pneumonias, soft tissue infections, bacteremia/septicemia, osteomyelitis, wound infections and pyodermas.

Effective in vitro against the following organisms (isolated from clinical infections listed above):

Organism	*Sensitive*	*Resistant*	*% Sensitive*
Staphylococci*	181	1	*99.4*
Streptococci	65	1	*98.5*
D. pneumoniae	14	0	*100.0*
Coliforms	34	3	*91.8*
Proteus	5	5	*50.0*
A. aerogenes	8	0	*100.0*
Ps. aeruginosa	5	4	*55.5*

*Includes many strains resistant to antibiotics.

As with all nitrofurans in *years* of extensive clinical use, there is little or no development of bacterial resistance with ALTAFUR.

NITROFURANS—a unique class of antimicrobials—
neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

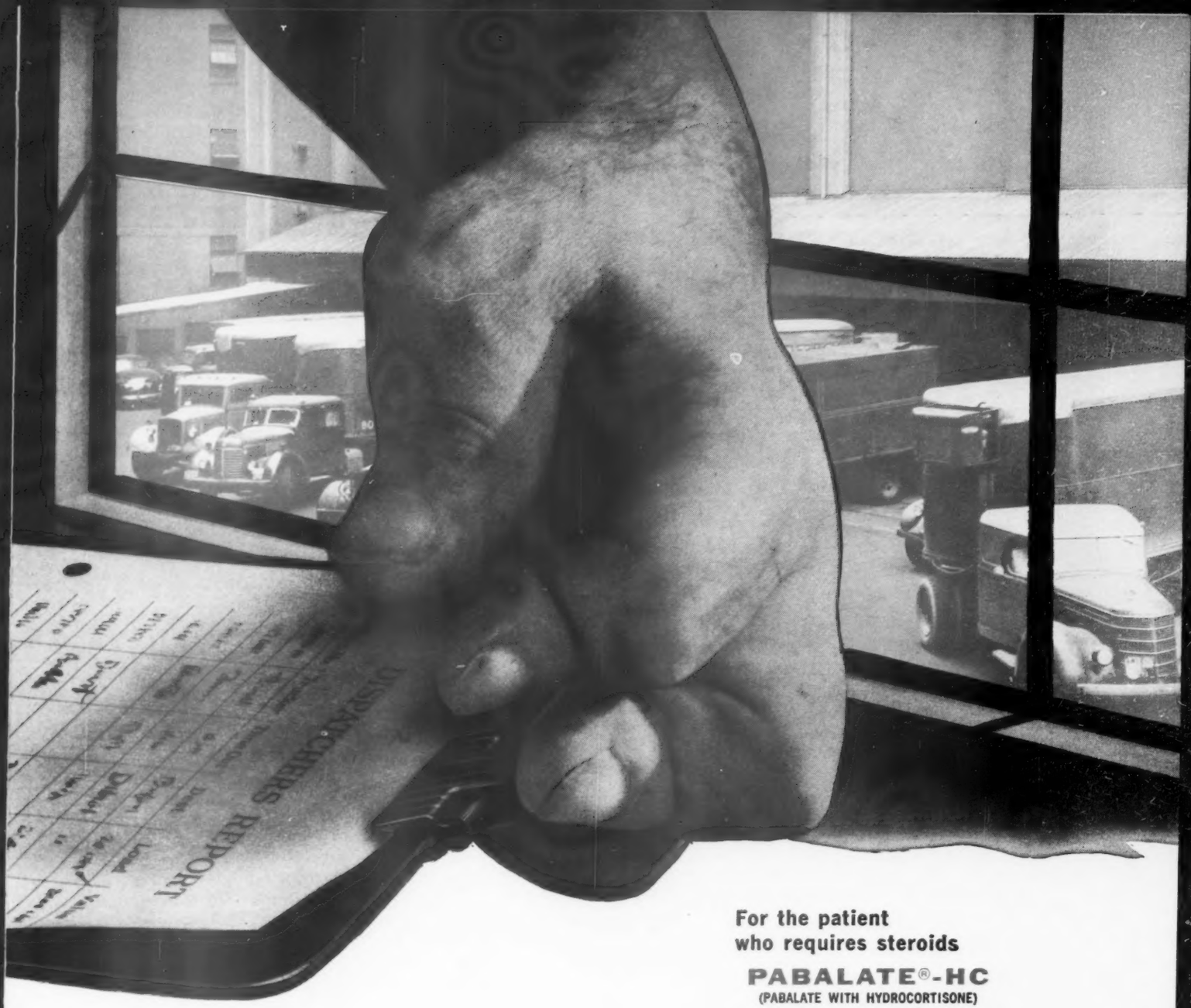


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on the job again

through effective relief and rehabilitation

Robins



For the patient who does not require steroids

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Reciprocally acting nonsteroid antirheumatics . . . more effective than salicylate alone.

In each enteric-coated tablet:

Sodium salicylate U.S.P.....0.3 Gm. (5 gr.)
Sodium
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Ascorbic acid .....50.0 mg.

or for the patient who should avoid sodium

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Ascorbic acid .....50.0 mg.

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PABALATE®-HC

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Comprehensive synergistic combination of steroid and nonsteroid antirheumatics... full hormone effects on low hormone dosage . . . satisfactory remission of rheumatic symptoms in 85% of patients tested.

In each enteric-coated tablet:

Hydrocortisone (alcohol) ..... 2.5 mg.
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Potassium para-aminobenzoate.. 0.3 Gm.
Ascorbic acid .....50.0 mg.

PABALATE® Robins PABALATE-HC

For steroid or non-steroid therapy: SAFE DEPENDABLE ECONOMICAL

A. H. ROBINS CO., INC., RICHMOND 20, VIRGINIA • Ethical Pharmaceuticals of Merit since 1878

the first major breakthrough
in the prophylactic management
of pain in angina pectoris

Marplan

- *clinically safer*
- *therapeutically more useful*

a new, more active
amine oxidase regulator
which has proven highly valuable
in the symptomatic relief
of angina pectoris

In approximately 70% of cases, Marplan

- reduces the frequency of anginal attacks
- improves exercise tolerance
- lowers nitroglycerin dependence

Ten critical
Marplan

1. What is Marplan? Marplan is a hydrazine derivative with marked potency in regulating the amine oxidase enzyme system. Already evaluated in over 4,000 patients, Marplan has demonstrated marked beneficial effects in the treatment of angina pectoris. Evidence to date indicates that Marplan may also be therapeutically valuable in a number of other important acute and chronic medical conditions. Chemically, Marplan is 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine.

2. What is the effect of Marplan in angina pectoris? Continued prophylactic administration of Marplan provides symptomatic relief—in the form of pain control and reduced nitroglycerin requirements—in approximately 70 per cent of cases.[1-3] "Excellent effects with relatively small doses" are reported in a group of 31 patients with angina pectoris. In that study, Marplan "afforded greater relief than any other compound in our experience."[3] To date, Marplan prophylaxis has been evaluated in a total of 238 anginal cases. The response rate was 72.7 per cent, with improvement ranging from a reduction in the number of attacks to virtual abolition of the anginal state.[1]

3. What is the effect of Marplan on blood pressure? Marplan should not be used as a hypotensive agent. The possibility of postural hypotension, though relatively infrequent, must be borne in mind.

4. What type of angina case is particularly responsive to Marplan prophylaxis? Marplan has been evaluated in angina of varying severity. It is felt, however, that optimum benefit will be derived in moderately severe to intractable cases.

5. Is the antianginal effect of Marplan the same as its antidepressant action? Marplan is unique in that it exhibits two distinct primary effects: its antianginal action, while biochemically related, is clinically separate from its antidepressive effects.

6. How can one compound have two such seemingly dissimilar effects? The mechanism of action of Marplan and of the other amine oxidase regulators is not yet fully defined. Marplan's pharmacologic effects are secured indirectly: By regulating amine oxidase levels; it inhibits the breakdown of serotonin, norepinephrine and other biologically active amines. In animal experiments, serotonin infusion of the heart muscle produces an increase in the ratio of coronary blood flow to coronary vascular resistance.[4]

7. How should Marplan be given? The usual starting dose is 30 mg daily to be given in single or divided doses. The patient should be observed carefully and individual dosage adjustment made according to response. Many patients will respond quickly to the initial dose of 30 mg daily, and the dosage should then be reduced to 10 or 20 mg daily (or less) for maintenance therapy. In some patients beneficial effects may not be observed for three or four weeks. Since daily doses larger than 30 mg may cause an increase in side effects, such as hypotension and constipation, it is not recommended that higher dosages be employed.

8. What are the precautions? All patients treated with hydrazine derivatives should be

questions define the scope of prophylaxis in angina pectoris

kept under close medical supervision. While there is no definite knowledge of a hazard with Marplan, use of this class of agent should be discontinued at the first sign of jaundice or impaired liver function. Periodic liver function tests are advised during hydrazine therapy. These drugs are contraindicated in patients with a history of previous liver disease or impaired liver function. In patients with impaired kidney function, Marplan should be used cautiously to prevent accumulation and should not be used in epileptic patients. Patients receiving a hydrazine in conjunction with drugs such as alcohol, ether, barbiturates, meperidine, cocaine, procaine, and phenylephrine should be more closely supervised.

9. What are the side effects, if any? In one of the largest bodies of clinical material for this new class of drugs, Marplan shows one of the lowest recorded incidences of side effects. Particular attention was focused on attempts to define as precisely as possible amine oxidase inhibitor side effects on a wide range of organs, including liver and bone marrow. Extensive clinical studies have revealed no jaundice or liver damage attributable to Marplan. Nevertheless, since Marplan is an amine oxidase inhibitor, the same precautions should be observed with Marplan therapy as with other amine oxidase inhibitors. Since Marplan is a potent therapeutic agent affecting many enzyme systems of the body, side effects may be expected to occur in a certain percentage of cases. Side effects have rarely been severe enough to necessitate discontinuance of Marplan therapy. However, as with all agents of this type, the patient should be observed for signs of orthostatic hypotension, complaints of dizziness and vertigo, constipation, overactivity, jitteriness, insomnia, peripheral edema, weakness, fatigue, dryness of the mouth, blurred vision and skin rashes.

10. How can patients be transferred from their present anginal prophylaxis? Initially the established nitrite regimen should be maintained, while simultaneously placing the patient on a daily dose of 30 mg Marplan. The patient is to be observed carefully and nitrite intake decreased as pain episodes diminish. Marplan prophylaxis should be continued for at least three or four weeks before evaluating the response.

Supplied: 10-mg tablets in bottles of 100 and 1,000.

References: 1. Clinical reports on file, Roche Laboratories. 2. W. Hollander and R. W. Wilkins in J. H. Moyer, Ed., *Hypertension*, Philadelphia, W. B. Saunders Co., 1959, p. 399. 3. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 4. C. W. Crumpton, et al., Conference on Amine Oxidase Inhibitors, New York City, November 20-22, 1958.

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MARPLAN™—brand of isocarboxazid

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Marplan

Tofrānil® a thymoleptic

brand of imipramine HCl

Specific in Depression

does

Produce remission or improvement in 70-85% of cases

Act effectively in all types of depression

Afford equally good results in severe as in mild cases

Achieve therapeutic benefit with minimal risk of serious side reaction

Indications for Tofrānil include:

Endogenous Depression, Reactive Depression, Involutional Melancholia, Senile Depression, Depression associated with other Psychiatric Disorders.

Availability: Tofrānil (brand of imipramine HCl) tablets of 25 mg. bottles of 100. Ampuls of 25 mg. (for intramuscular administration only) cartons of 10 and 50.

.....not a MAO inhibitor

does not

Inhibit monoamine oxidase either in brain or liver with its associated risks

Produce dangerous potentiation of other drugs such as barbiturates and alcohol

Act by producing undesirable central nervous stimulation leading to agitation and excitement

Cause disturbance of color vision

The efficacy of Tofranil is attested by more than 50 published reports and confirmed by clinical experience in more than 50,000 cases.

Detailed Literature Available on Request.

Geigy, Ardsley, New York

Geigy

reduces anginal attacks and fear of attacks

protects against pain by sustained coronary vasodilatation and control of complicating and triggering emotions

reduces fear of attacks
reduces severity of attacks
reduces frequency of attacks
reduces dependence on nitroglycerin
increases workload tolerance

Supplied: Tablets, vials of 50. Each tablet contains 200 mg. of meprobamate and 10 mg. of pentaerythritol tetranitrate.

EQUANITRATE®

Meprobamate and Pentaerythritol Tetranitrate, Wyeth

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"In all things, success depends upon previous preparation..."
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ELDEC® KAPSEALS®

vitamin-mineral-hormone supplement

help prepare your middle-aged patients for healthy retirement years

each KAPSEAL *contains:*

vitamins	
Vitamin A	1,667 Units (0.5 mg.)
Vitamin B_1 mononitrate	0.67 mg.
Ascorbic acid	33.3 mg.
Nicotinamide	16.7 mg.
Vitamin B_2	0.67 mg.
Vitamin B_6	0.5 mg.
Vitamin B_{12} with intrinsic factor concentrate	0.033 USP Unit (oral)
Folic acid	0.1 mg.
Choline bitartrate	6.67 mg.
Pantothenic acid (as the sodium salt)	5 mg.
minerals	
Ferrous sulfate (exsiccated)	16.7 mg.
Iodine (as potassium iodide)	0.05 mg.
Calcium carbonate	66.7 mg.
digestive enzymes	
Taka-Diastase® (aspergillus oryzae enzymes)	20 mg.
Pancreatin	133.3 mg.
protein improvement factors	
l-Lysine monohydrochloride	66.7 mg.
dl-Methionine	16.7 mg.
gonadal hormones	
Methyl testosterone	1.67 mg.
Theelin	0.167 mg.

dosage: One Kapseal three times daily before meals. Female patients should follow each 21-day course with a 7-day rest interval.

packaging: ELDEC KAPSEALS are available in bottles of 100.

PARKE, DAVIS & COMPANY, DETROIT 32, MICHIGAN

ELDEC BEGINS AT 40

90259



Before Esidrix:
Weight 176 lbs.

27 pounds lost in 19 days; ascites and

RECORD OF TREATMENT (At a leading New York City hospital. Photos used with permission of the patient.)

Date	3/3	3/4	3/5	3/6	3/7	3/8	3/9	3/10	3/11	3/12	3/13	3/14	3/15	3/16	3/17	3/18	3/19	3/20	3/21	3/22	3/23
Weight (pounds)	178	176	170	169	167	159	158	158	157	153	155	155	156	154	153	154	153	—	—	151	149
Rx	M*		Esidrix 50 mg. b.i.d.																		

*Mercurial diuretic



Esidrix T.M.

(hydrochlorothiazide CIBA)

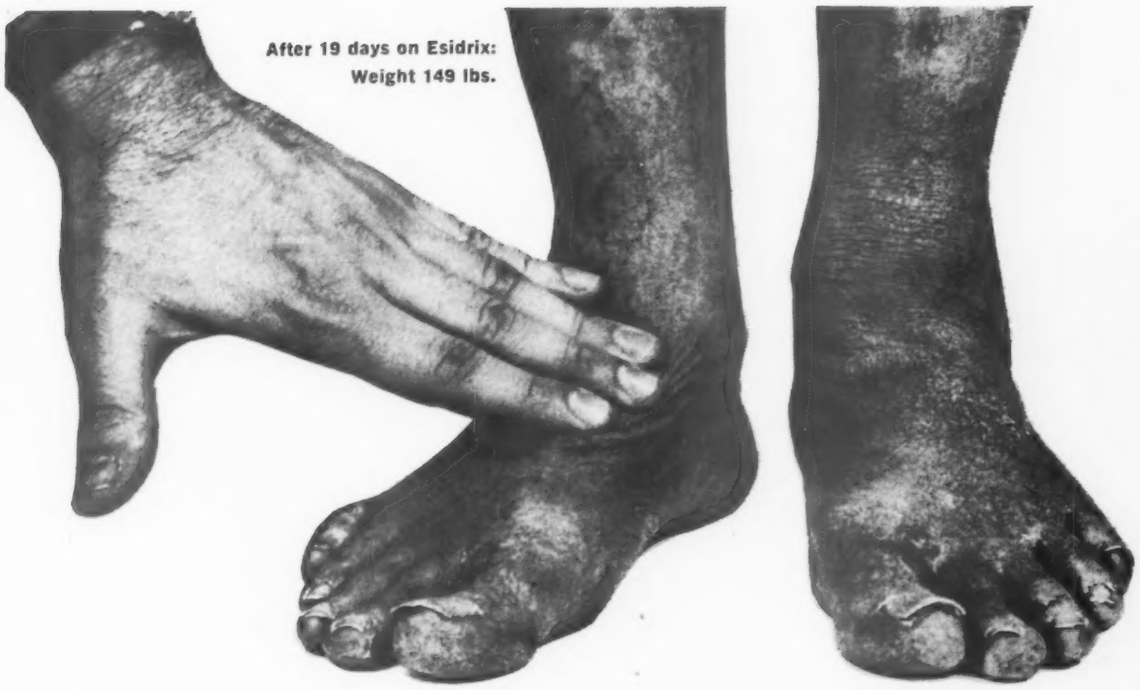


pre-eminently effective whenever diuresis is desired

Indicated in: congestive heart failure . . . nephrosis and nephritis . . . toxemia of pregnancy . . . premenstrual edema . . . edema of pregnancy . . . steroid-induced edema . . . edema of obesity

Supplied: Esidrix *Tablets,*
25 mg. (pink, scored)
and 50 mg. (yellow, scored);
bottles of 100 and 1000.

CIBA
SUMMIT, N. J.



pedal edema reduced with Esidrix

H. K., 44 years old, was admitted to the hospital on 3/3/59 with complaints of *swollen abdomen, swelling of both legs and exertional dyspnea.* These symptoms had been intensifying over a three-week period. The patient's history included heavy drinking since the age of 18, and one prior admission to the hospital in 1954 with ascites and pedal edema. Diagnosis, at that time, was Laennec's cirrhosis, and the patient responded well to a regimen of diuretics, salt restriction and multivitamins. There was no recurrence up to that leading to his current admission.

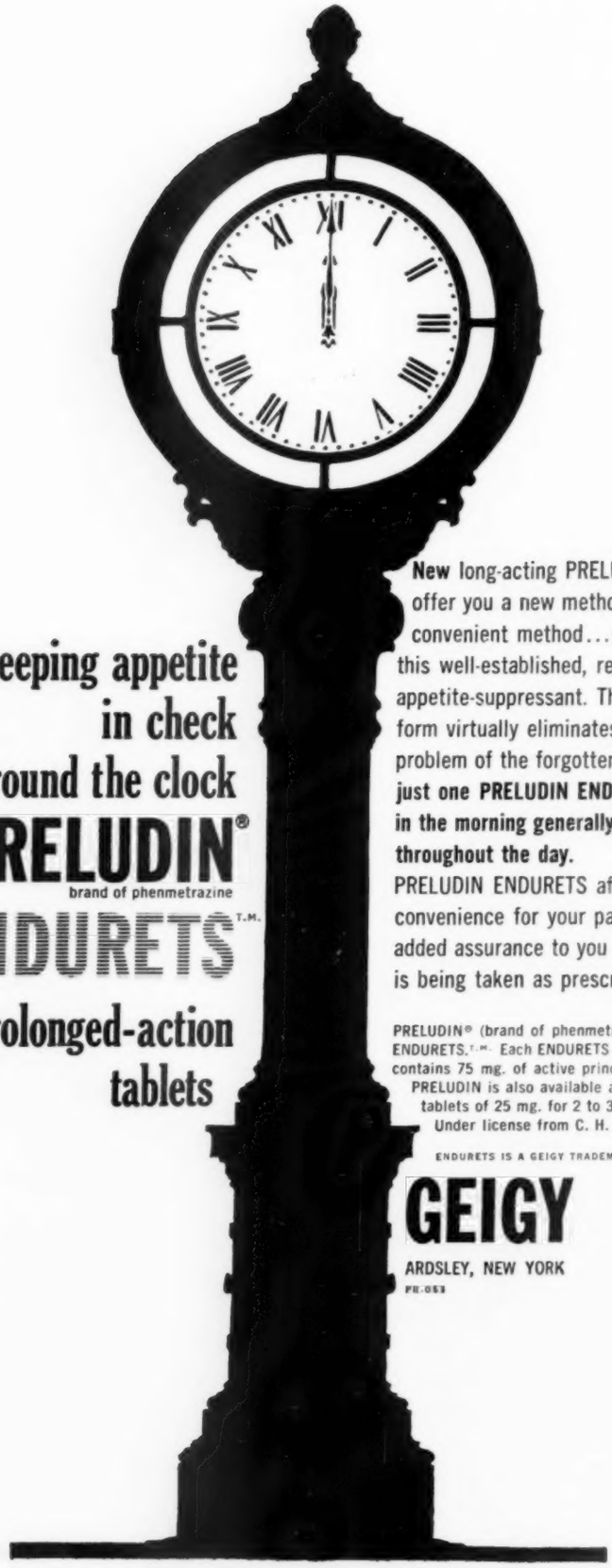
2/2714HK



Clinical findings worthy of note: Eyes — conjunctivae and sclerae slightly icteric. Chest—diaphragm elevated. Abdomen — girth enlarged, definite fluid wave. Liver palpated 4 fingerbreadths below the costal margin; no other palpable viscera. Extremities—pedal edema (4+).

The patient is well developed and not in acute distress. Blood pressure, 140/80 mm. Hg; pulse, 112/min.; respiration, 20/min. Impression: Laennec's cirrhosis—decompensated.

Treatment: Mercurial diuretic on 3/3 and 3/4, followed by Esidrix, 50 mg. b.i.d., from 3/5 to 3/23 when patient signed out of hospital. Esidrix induced copious diuresis resulting in almost complete disappearance of edema.



keeping appetite
in check
around the clock

PRELUDIN®
brand of phenmetrazine

ENDURETS™

prolonged-action
tablets

New long-acting PRELUDIN ENDURETS offer you a new method... a more convenient method... of administering this well-established, reliable appetite-suppressant. The new ENDURETS form virtually eliminates the vexing problem of the forgotten dose because... **just one PRELUDIN ENDURET taken in the morning generally curbs the appetite throughout the day.**

PRELUDIN ENDURETS afford greater convenience for your patient... added assurance to you that medication is being taken as prescribed.

PRELUDIN® (brand of phenmetrazine hydrochloride) ENDURETS.™ Each ENDURETS prolonged-action tablet contains 75 mg. of active principle.

PRELUDIN is also available as scored, square pink tablets of 25 mg. for 2 to 3 times daily administration.

Under license from C. H. Boehringer Sohn, Ingelheim.

ENDURETS IS A GEIGY TRADEMARK

GEIGY

ARDSLEY, NEW YORK

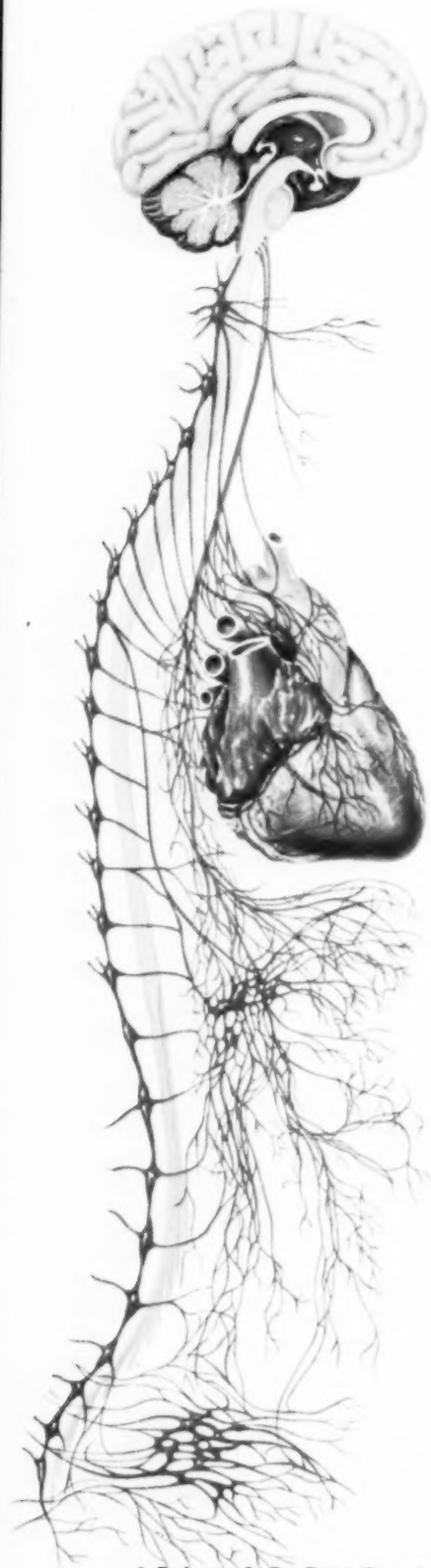
PE-053

Sleepy . . . sleepier . . . asleep! Placidyl's light touch does the trick. Brief. Effective.
Not a barbiturate. Your patients sleep soundly, wake next morning refreshed. Put Placidyl to work in your own practice, soon.

ABBOTT



Placidyl® nudges your patient to sleep
(Ethchlorvynol, Abbott)



and the evidence mounts

In two recent studies, involving 179 mixed anxiety and hypertensive patients—Harmonyl produced far less lethargy and listlessness than Reserpine—and yet with comparable potency and effectiveness. Below, two charts taken from these reports dramatically illustrate the exceptionally low incidence of side reactions with Harmonyl.

RESULTS OF "DOUBLE-BLIND" STUDY OF 99 MIXED ANXIETY AND TENSION PATIENTS[1]

Side Effects	Tablet A Deserpidine 43 patients	Tablet C Placebo 24 patients	Tablet C Reserpine 27 patients
DIZZINESS	0 (0%)	3 (12%)	4 (15%)
DRYNESS OF MOUTH	3 (7%)	1 (4%)	6 (22%)
BIZARRE DREAMS	0 (0%)	2 (8%)	7 (26%)
LISTLESSNESS	1 (2%)	4 (17%)	9 (33%)
DETACHMENT (Diminished awareness)	0 (0%)	0 (0%)	2 (7%)
ANOREXIA	1 (2%)	3 (12%)	4 (15%)
WEAKNESS, TIREDNESS, NO PEP	0 (0%)	8 (33%)	16 (59%)
DAYTIME SLEEPINESS	1 (2%)	4 (17%)	19 (70%)
HEADACHE	0 (0%)	18 (75%)	4 (15%)
NAUSEA	0 (0%)	2 (8%)	3 (11%)
ABDOMINAL CRAMPS	1 (2%)	4 (17%)	5 (18%)
RASH	0 (0%)	0 (0%)	0 (0%)
NASAL STUFFINESS	1 (2%)	0 (0%)	4 (15%)
LOOSE STOOLS	0 (0%)	1 (4%)	3 (11%)

Percentages supplied by Abbott Laboratories.

Author's Comments: "With deserpidine there was less abrupt hypotensive action on blood pressure than with reserpine, and less fatigue or sleepiness during the day."

COMPARISON OF SIDE EFFECTS IN 80 HYPERTENSIVES TREATED WITH VARIOUS FORMS OF RAUWOLFIA[2]

Side Effects	Reserpine	Alseroxylon	Deserpidine	Rescinnamine
LETHARGY	11	10	1	1
NASAL OBSTRUCTION	10	8	8	2
DREAMS	8	7	3	1
ACHING	8	7	3	0
DEPRESSION	3	3	0	1
DIARRHEA	2	3	1	0

Author's Comments: "Deserpidine when given in the morning, showed a definitely lower incidence of lethargy, and depression was not encountered in any patient."

1. Frohman, I. P., Tranquilizers in General Practice and Clinical Evaluation of Deserpidine, an Alkaloid of Rauwolfia Canescens, M. Ann. District of Columbia, 27:641, December, 1958.

2. Winsor, T., Comparative Effects of Various Rauwolfia Alkaloids in Hypertension, Diseases of the Chest, April, 1959.

908050

Harmonyl®

(Deserpidine, Abbott)

for your next working hypertensive

ABBOTT



IT HAPPENS IN THE BEST OF FAMILIES NOURISHED

VITERRA®

meets the specific vitamin-mineral needs of every member of the household — select the form that suits the age and condition of each patient best

VITERRA CAPSULES—comprehensive daily supplement. Bottles of 100.

VITERRA TASTITABS®—can be chewed, dissolved, or swallowed. Bottles of 100.

VITERRA THERAPEUTIC—high potency formula. Bottles of 30 and 100.

VITERRA PEDIATRIC—for infants and small children. 50 cc. Metered-Flow bottle.

Selectively formulated by one of the major producers of bulk vitamins

ROERIG Rx

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

In Asthma

The Most Important Word to Remember...

Medihaler

automatically measured-dose aerosol medications

Nonbreakable • Shatterproof • Spillproof • Leakproof

Available with either epinephrine or isoproterenol



Medihaler-EPI

Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.15 mg. epinephrine.

Medihaler-ISO

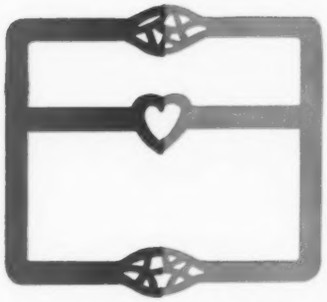
Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.06 mg. isoproterenol.



NOTABLY SAFE AND EFFECTIVE FOR CHILDREN, TOO

Riker

NORTHRIDGE, CALIFORNIA



FOR GREATER LATITUDE IN SOLVING THE PROBLEM

HYPERTENSION

WITHOUT SIGNIFICANT POTASSIUM DEPLETION

NEW

RAUTRAX, a combination of Raudixin with Ademol (flumethiazide)—**the new, safe nonmercurial diuretic**—controls all degrees of hypertension. Elimination of excess extracellular sodium and water is rapid and safe.[1-5] Potassium loss is less than with other nonmercurial diuretics;[1-3] and, in addition, Rautrax increases protection against potassium and chloride depletion during long-term management by including supplemental potassium chloride.

The dependable diuretic action of Ademol rapidly controls the clinical and subclinical edema often associated with cardiovascular disease. And after Rautrax has normalized the fluid balance, the normal serum electrolyte pattern is not altered appreciably by continued administration.[4] Ademol also potentiates the antihypertensive action of Raudixin.[1] In this way a lower dose of each component controls hypertension effectively and safely . . . with fewer side effects.

REFERENCES: 1. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: New England J. Med. 260:872 (April 23) 1959. 2. Fuchs, M.; Bodi, T., and Moyer, J. H.: Am. J. Cardiol. 3:676 (May) 1959. 3. Fuchs, M., and others: Monographs on Therapy 4:43 (April) 1959. 4. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: Am. Heart J. 57:484 (April) 1959. 5. Rochelle, J. B., III; Montero, A. C., and Ford, R. V.: Antibiotic Med. & Clin. Ther. 6:267 (May) 1959. LITERATURE AVAILABLE ON REQUEST

SQUIBB

Squibb Quality—
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RAUDIXIN (Squibb standardized whole root Rauwolfia Serpentina) / ADEMOL (Squibb Flumethiazide) / POTASSIUM CHLORIDE

'RAUDIXIN,' ®, 'RAUTRAX' AND 'ADEMOL' ARE SQUIBB TRADEMARKS



The tyranny of the clock

For many diabetics, time is a tyrant. No matter how inconvenient it may be, they must take their meals and injections "by the clock," or risk extremely disquieting reactions.

Orinase® makes it possible for you to lift this burden from most of these insulin-dependent patients. Given in conjunction with insulin, it smooths out the "peaks and valleys" of erratic blood sugar levels . . . "stabilizes" a surprising percentage of brittle diabetics.

At the same time, it may enable you to reduce the insulin dosage for many insulin-dependent diabetics. ®TRADEMARK, REG. U. S. PAT. OFF. — TOLBUTAMIDE, UPJOHN

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Upjohn **ORINASE**



In senile anxiety

VISTARIL® hydroxyzine pamoate

helps you calm him—safely

PRONOUNCED CALMING ACTION: "Among the agitated seniles [treated with hydroxyzine]...75 percent showed improved conduct and interpersonal relations..."[1]

PROVEN SAFETY: In many long-term studies, hydroxyzine [Vistaril] has been administered to thousands of patients for extended periods without any toxic or untoward reactions.[2-7]

One 50 mg. tablet of Vistaril q.i.d. will help your next patient suffering from anxiety problems to renew normal relationships with other human beings.

Pfizer *Science for the world's well-being*

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Brooklyn 6, N.Y.

REFERENCES: 1. Settel, E.: Am. Pract. & Digest Treat. *8*:1584 (Oct.) 1957. 2. Smigel, J. O., et al.: J. Am. Geriatrics Soc. *7*:61 (Jan.) 1959. 3. Ayd, F. J., Jr.: New York J. Med., *57*:1742-1747 (May 15) 1957. 4. Cohen, S.: Am. Pract. & Digest Treat. *8*:946-947, (June) 1957. 5. Shalowitz, M.: Geriatrics, *2*:312-315 (July) 1956. 6. Ayd, F. J., Jr.: International Symposium on Psychotropic Drugs, Milan (May) 1957. 7. Garber, R. C., Jr.: J. Florida M. A., *45*:549-552 (Nov.) 1958.

REFLECTION ON CORTICOTHERAPY:



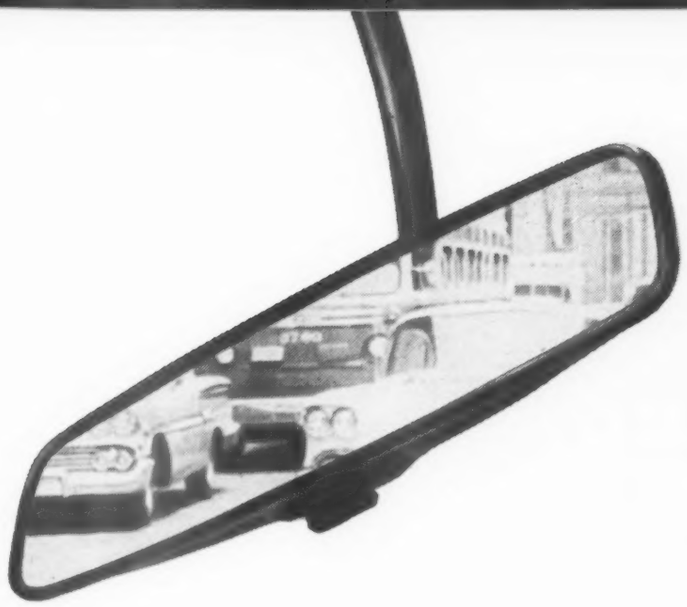
Particularly in corticotherapy, the intent is not to treat diseases, but to treat patients. This intent is best served by using the steroid that has the best ratio of desired effects to undesired effects:

Medrol*

the corticosteroid that hits the disease, but spares the patient

Upjohn THE UPJOHN COMPANY
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*TRADEMARK, REG. U. S. PAT. OFF. — METHYLPREDNISOLONE, UPJOHN



Traffic: jammed

Car: stalled

Temper: mild

Ulcer: quiet

Here's a man whose ulcer once would have protested strongly—not just at traffic problems—but at the entire gamut of stress to which modern man is subjected.

His physician, aware that *the patient as well as the ulcer* must be treated, has prescribed ALUDROX SA.

eases tension • promotes healing
relieves pain • reduces acid secretion
inhibits gastric motility

ALUDROX® SA

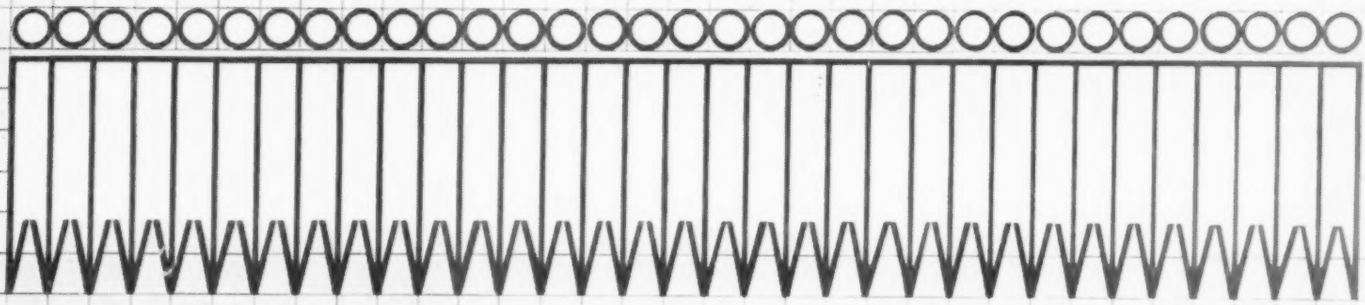
Suspension and Tablets: Aluminum Hydroxide Gel with Magnesium Hydroxide, Ambutonium Bromide and Bufabarbital, Wyeth

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Philadelphia 1, Pa.

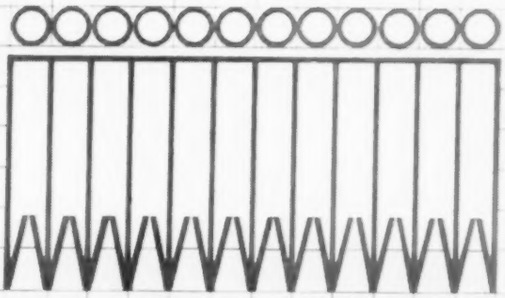
Decadron®

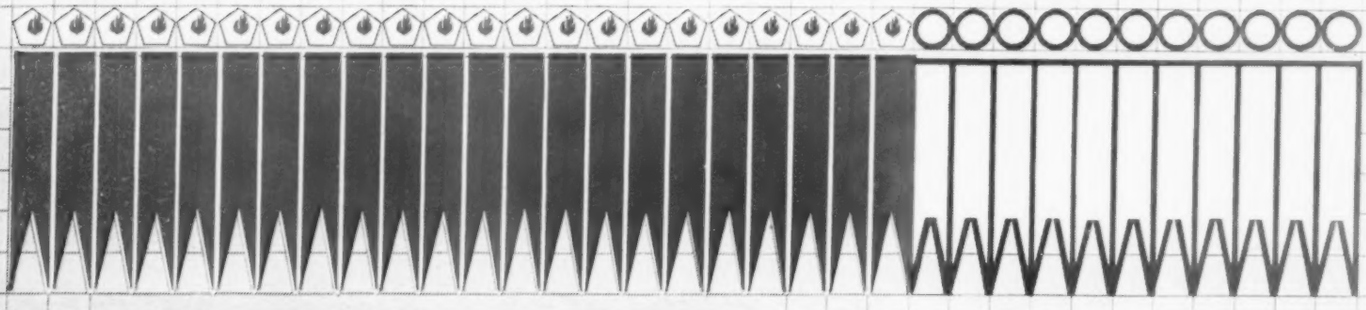
DEXAMETHASONE

treats more patients more effectively...

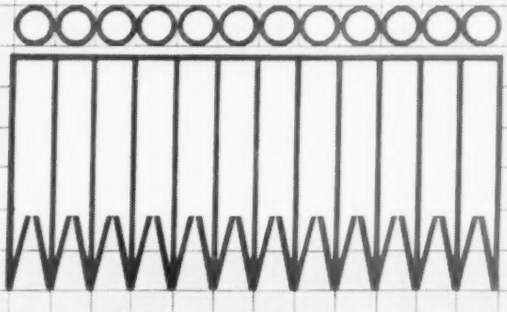


Of 45 arthritic patients
who were refractory
to other corticosteroids*





22 were successfully treated with **Decadron**[1,2]



1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

*Cortisone, prednisone and prednisolone.

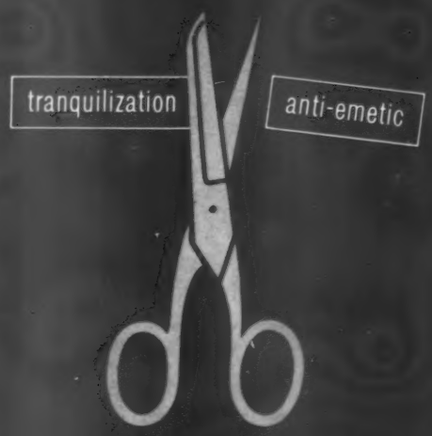
DECADRON is a trademark of Merck & Co., Inc.

Additional information on DECADRON is available to physicians on request.

Merck Sharp & Dohme

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

now potent tranquilizer therapy is safer than ever



Virtual freedom of Mellaril from major toxic effects is due to greater specificity of tranquilizing action – divorced from such "diffuse" effects as anti-emetic action.

MELLARIL is virtually free of such toxic effects as

- jaundice
- Parkinsonism
- blood dyscrasia

"Thioridazine [MELLARIL] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines. . . . This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."

SANDOZ

Mellaril®

THIORIDAZINE HCl

specific, effective tranquilizer • safer at all dosage levels

remarkable lack of side effects

In more than 3,000 carefully-followed patients, Mellaril has been almost completely free of such major side effects as jaundice, extrapyramidal symptoms, Parkinsonism, blood dyscrasia, dermatitis– **even when given in quantities far in excess of the usual dosage.**

"POVERTY" OF SIDE EFFECTS

"The most striking aspect of thioridazine [Mellaril] therapy is the poverty of side effects.... In its lack of side effects and low toxicity, it is superior to all other tranquilizing drugs tested. For this reason also it is well tolerated by patients, particularly those who are not hospitalized and who frequently discontinue their medication because of dizziness, sleepiness, increased tension or parkinsonism with other drugs."[2]

NEGLIGIBLE SIDE EFFECTS

"Side effects were negligible at all dosage levels: no incidence of parkinsonism or other extrapyramidal symptoms. Minimal sedation, on the whole lower than with other tranquilizing agents. No alteration in liver function, urine or blood. No photosensitivity. Patient acceptability was exceptional: lack of drowsiness, lethargy or 'washed out' feeling, permitted patients to carry on normal everyday activities. Orthostatic hypotension was absent. The initial 'keyed up' tense feeling common to other drugs of this type was absent.... Patients forced to interrupt treatment with other phenothiazine derivatives because of parkinsonism or other extrapyramidal symptoms were able to continue therapy with thioridazine without appearance of parkinsonism."[3]

SINGULARLY FREE OF SIDE EFFECTS

"The extrapyramidal syndrome was not encountered in any of its forms. Dizziness and sleepiness responded to a reduction in dosage. Other side effects did not occur.... It is singularly free from the side effects ordinarily seen with these [phenothiazine] compounds."[4]

ABSENCE OF SIGNIFICANT SIDE EFFECTS

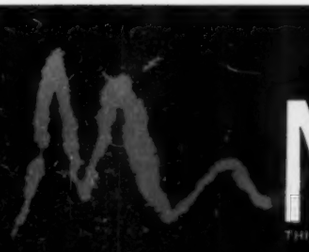
"None of the following toxic effects, so common after administration of the phenothiazines, was present during the period of Thioridazine administration: Parkinsonism or Parkinson-like symptoms, photosensitivity, orthostatic hypotension, bone-marrow depression."[1]

MINIMAL SIDE EFFECTS

"Side effects such as extrapyramidal activity, jaundice and photosensitivity have not been observed in patients treated with Thioridazine [Mellaril]. Extrapyramidal side effects produced by other phenothiazines have disappeared promptly with no deterioration in the behavioral response when these patients have been shifted to Thioridazine."[5]

NO JAUNDICE

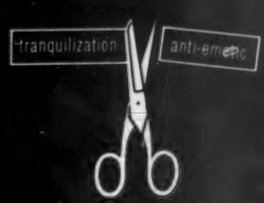
"No allergic reactions were observed such as skin eruptions, jaundice or agranulocytosis. Central nervous system toxicity, as manifested by extrapyramidal effects, seizures, and excitement did not occur despite the use of high doses (up to 2000 mg.) of the drug."[6]



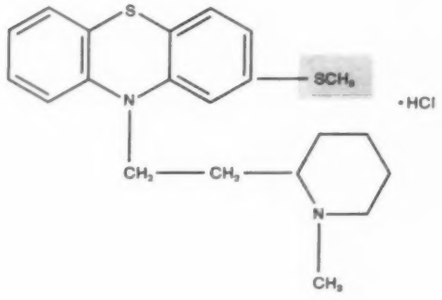
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THIORIDAZINE HCl

specific, effective tranquilizer • safer at all dosage levels

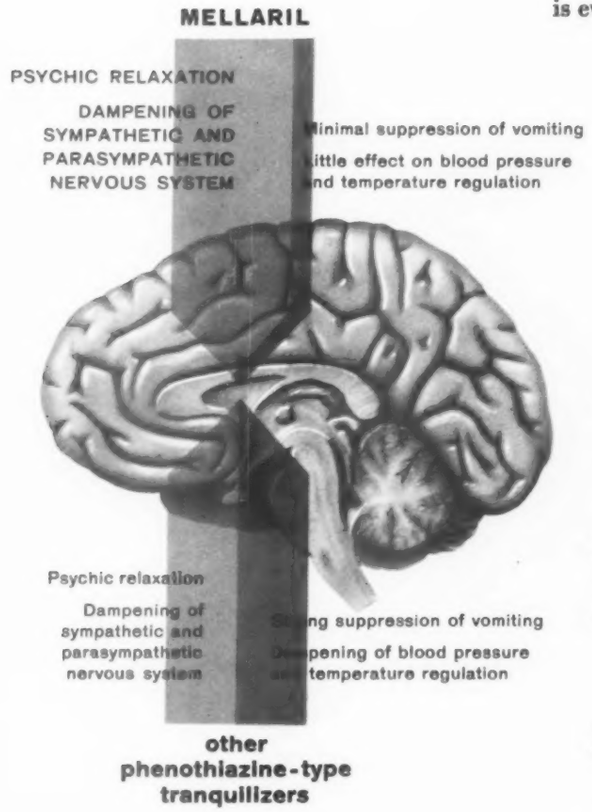


a new advance in tranquilization:
greater specificity of tranquilizing action plus fewer side effects



Of 109 phenothiazines synthesized by Sandoz, Mellaril was selected as the most promising on the basis of extensive evaluation. The presence of a thiomethyl radical (S-CH$_3$) in the position conventionally occupied by a halogen in other phenothiazines is unique and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:

1 **A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.**





2 **Less "spill-over" action to other brain areas – hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.**

3 **A notable absence of extrapyramidal stimulation.**

4 **Lack of impairment of patient's normal drive and energy, while achieving psychomotor control in mental and emotional disorders.**

5 **Virtual freedom from toxic effects – jaundice, photosensitivity, skin eruptions, disturbed body temperature regulation, blood forming disorders have been absent in reports currently available.**

These properties add up to a greater margin of safety in general office practice, in ambulatory psychiatric out-patient clinics, and in hospitalized patients.

Mellaril®

THIORIDAZINE HCl

specific, effective tranquilizer • safer at all dosage levels



excellent clinical response

In office practice and in hospitalized patients, Mellaril has proved highly useful for a wide variety of major and minor emotional disorders (such as anxiety, tension, apprehension, alcoholism, agitated psychoneurosis, agitated psychotic states, etc.).

EXTREMELY SATISFACTORY ". . . produced extremely satisfactory results in the broad therapeutic range represented in this series."[3]

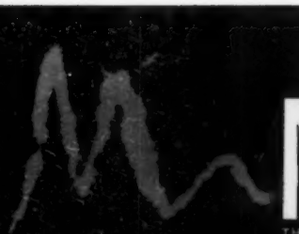
POTENT AGENT ". . . appears to be a potent agent in the symptomatic management of a variety of psychiatric states."[4]

MAJOR ADDITION TO THERAPEUTICS "This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."[1]

AN ACTIVE AGENT "Thioridazine is an active therapeutic agent. . . . It is effective in a variety of psychiatric disorders, including schizophrenic reactions. . . . The drug is particularly advantageous for a group of schizophrenic patients who are sometimes made worse by other phenothiazine derivatives or Rauwolfia alkaloids. It should also be suitable for treating patients with psychoneuroses and chronic brain syndrome."[6]

EVEN IN VERY SEVERE CASES "Of the 152 patients treated 25 have been released and they have not suffered a relapse. This proportion is significant if we stop to consider that we are dealing only with acute cases which had been considered hopeless and obviously destined to finish their days in an asylum."[7]

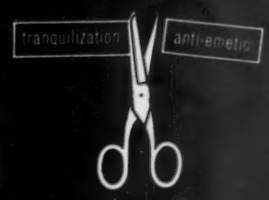
EXCELLENT THERAPEUTIC RESPONSE "Patients with emotional tensions resulting from the stress and strain of life . . . were treated with Mellaril at the dosage level of 10 mg. three times daily. In 94 such patients, 83 obtained an excellent therapeutic response."[8]



Mellaril®

THIORIDAZINE HCl

specific, effective tranquilizer • safer at all dosage levels



"...extremely satisfactory results..." in a clinical spectrum ranging from minor nervous disorders to severe psychotic disturbances[3]

RESULTS WITH MELLARIL IN 194 PATIENTS[3]

ACUTE PSYCHOTICS	CHRONIC PSYCHOTICS	NEUROTICS
83% satisfactory effect	68% satisfactory effect	57% satisfactory effect
Some cases had complete remission of symptoms. Most were able to return home to useful occupations.	Relief of symptoms in cases permitted easier management and a return to a more or less useful life.	Some cases, complete relief of symptoms. Other cases, partial relief of symptoms.

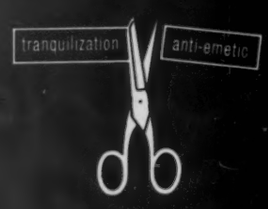
RESULTS WITH MELLARIL IN PATIENTS PREVIOUSLY TREATED WITH OTHER TRANQUILIZERS[3]

DIAGNOSTIC CATEGORY	IMPROVED %	VERY SATISFACTORY %	SATISFACTORY %	UNSATISFACTORY %
SCHIZOPHRENIA				
Acute	89	61	28	11
Chronic paranoid	84.2	31.6	52.6	15.8
Chronic, other	73.9	21.7	52.2	26.1
Residual	57.1	9.5	47.6	42.9
CHRONIC BRAIN SYNDROME	66.6	33.3	33.3	33.3
CHRONIC PSYCHONEUROSIS	62.5	12.5	50	37.5
CHRONIC PSYCHOSOMATIC DISORDERS	75	25	50	25

Mellaril®

THIORIDAZINE HCl

specific, effective tranquilizer • safer at all dosage levels



a guide to administration and dosage

Dosage ranges from 10 mg. three or four times a day in milder situations to 25 mg. three or four times a day for more disturbed patients. In ambulatory psychiatric out-patients, dosages of 50 to 100 mg. three or four times a day have been found adequate. For severely disturbed hospitalized psychotics, dosages of 200 to 300 mg. three times a day may be administered.

Dosage must be individualized according to the condition and degree of response. In all cases, the smallest effective dosage should be determined for each patient.

INDICATION	USUAL STARTING DOSE	TOTAL DAILY DOSAGE RANGE
	ADULTS	
Mental and Emotional Disturbances:		
MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneurosis, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
	CHILDREN	
BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

PRECAUTIONS: Although possessing a unique structure and a selectivity of action which broadens its therapeutic ratio, the physician should be alert to the possibility of untoward reactions in certain susceptible individuals. In particular, he should watch for potential hemopoietic depression, jaundice or orthostatic hypotension. As with other phenothiazines, Mellaril is contraindicated in severely depressed or comatose states from any cause.

SUPPLIED: MELLARIL Tablets, 10 mg., 25 mg., 100 mg. Bottles of 100.

1. Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959. 2. Kinross-Wright, V. J.: Lecture, Clinical Meeting, American Medical Association, Minneapolis, Dec. 4, 1958. 3. Kinross-Wright, V. J.: Scientific Exhibit, Clinical Meeting, American Medical Association, Minneapolis, Dec. 2-5, 1958. 4. Cohen, S.: TP-21, a new phenothiazine, Am. J. Psychiat. *115*:358, Oct. 1958. 5. Glueck, B.: Scientific Exhibit, American Psychiatric Association, Philadelphia, April 27-May 1, 1959. 6. Hollister, L. E., and Macdonald, B. F.: Presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959. 7. Remy, M.: Schweiz. med. Wchnschr. *88*:1221, Nov. 29, 1958. 8. Freed, S. C., in discussion on Thioridazine (Mellaril) in Psychiatric Patients, Hollister, L. E., and Macdonald, B. F., presented at California Medical Association; Section on Psychiatry, San Francisco, Feb. 25, 1959.

- controls neurotic and psychotic patients with anxiety, apprehension, nervous tension
- virtual absence of jaundice, parkinsonism, photosensitivity, dermatitis
- minimal sedation and drowsiness
- does not mask organic conditions such as brain tumors, intestinal obstruction, etc., because of lack of anti-emetic action
- increased specificity of action results in greater safety at all dosage levels

SANDOZ

Mellaril®

THIORIDAZINE HCl

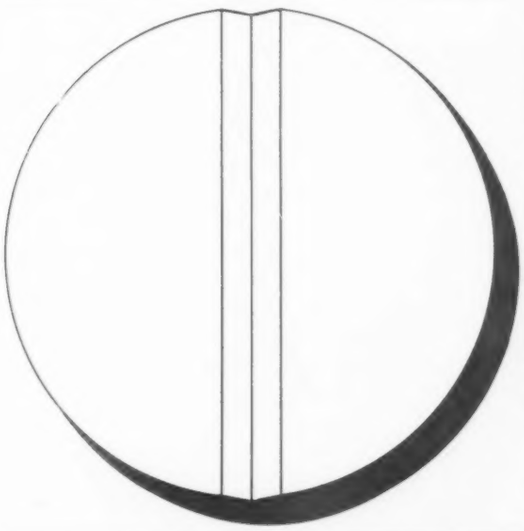
specific, effective tranquilizer • safer at all dosage levels



GREATER CONVENIENCE

DOUBLE POTENCY

AT LOW COST TO YOUR PATIENT



Pentids '400'

Squibb 400,000 units Buffered Penicillin G Potassium Tablets

For the treatment of penicillin susceptible infections—
ranging from **mild to moderately severe**—due to
hemolytic streptococcus / pneumococcus / staphylococcus /
and for the prevention of streptococcal infections where there is a history of rheumatic fever

Clinical effectiveness confirmed by millions of cases
Specific in many common infections
Daily dosage may be spaced without regard to mealtime
Ease of administration with oral penicillin
Economy for the patient

SQUIBB Squibb Quality—the Priceless Ingredient

new convenient oral tablets

PENTIDS '400,' each scored tablet contains 400,000 units of penicillin G potassium buffered, bottles of 12 and 100. Twice the unitage of Pentids 200,000 units.

also available

PENTIDS, 200,000 units of buffered penicillin G potassium per scored tablet, bottles of 12, 100, and 500.

PENTIDS FOR SYRUP, 200,000 units of penicillin G potassium per teaspoonful (5 cc.), 12 dose bottles.

PENTIDS, CAPSULES, 200,000 units of penicillin G potassium per capsule, bottles of 24, 100, and 500.

PENTIDS SOLUBLE TABLETS, 200,000 units of penicillin G potassium per tablet, vials of 12 and bottles of 100.

PENTIDS-SULFAS TABLETS, 200,000 units of penicillin G potassium with 0.5 Gm. triple sulfas per tablet, bottles of 30, 100, and 500.

PENTIDS® IS A SQUIBB TRADEMARK

NIAMID*

the mood brightener

EFFECTIVE AND WELL TOLERATED

in depression

NIAMID has been found to be strikingly effective and well tolerated in a broad range of depressive states including a wide variety of the milder depressive syndromes, as well as the masked depression so frequently seen in general practice. These syndromes include: depression associated with the menopause, postoperative depressive states and senile depression; depression accompanying chronic or incurable illness, such as gastrointestinal and cardiovascular disorders and inoperable cancer.

in angina pectoris

NIAMID, in intensive clinical tests, has proved to have a high degree of safety and to be a valuable adjunct in the management of the anginal syndrome. NIAMID produces striking symptomatic improvement in angina patients — markedly reduces the pain, severity and frequency of anginal episodes, reduces nitroglycerin requirements, and provides an increased sense of well-being. Since dramatic improvement is seen in some patients, it is wise to advise the patient against overexertion — his disorder still holds potential dangers despite relief of symptoms.

DOSAGE: Start with 75 mg. daily in single or divided doses. After a week or more, adjust the dosage, depending upon patient response, in steps of one or one-half 25 mg. tablet. Once improvement is seen, gradually reduce dosage to the maintenance level. Many patients respond to NIAMID within a few days, others in 7 to 14 days. A few patients may require as much as 200 mg. daily over a longer period of time before significant improvement is seen.

PRECAUTIONS: Side effects are infrequent and mild, and often lessened or eliminated by a reduction in dosage. Hypotensive effects have rarely been noted and no jaundice or other evidence of liver damage has been reported in patients receiving NIAMID. However, in patients with a history of liver disease, the possibility of hepatic reactions should be kept in mind.

SUPPLY: NIAMID is available as 25 mg. (pink) and 100 mg. (orange) scored tablets.

Already clinically proved in several thousand patients—

Complete references and a Professional Information Booklet giving detailed information on NIAMID are available on request.

Pfizer *Science for the world's well-being*

*Trademark for brand of nialamide

PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc., Brooklyn 6 New York



‘Deprol’ provides

COMPREHENSIVE TREATMENT



at three levels

1
hypothalamus

2
thalamus and limbic system

3
spinal cord

FOR DEPRESSION

AND ASSOCIATED ANXIETY AND PHYSICAL TENSION

"Features of anxiety commonly accompany depressive features, and not infrequently these anxiety symptoms, not those of the underlying and primary depression, are the presenting ones."

Yonge, K.A.: Depressions in disguise. Canad. M.A.J. *74*:693, May 1, 1956.

RELIEVES DEPRESSION
by improving mood and outlook without excessive stimulation or rebound depression. Relieves symptoms such as crying, lethargy, loss of appetite, insomnia.

RELIEVES ASSOCIATED ANXIETY
by reducing exaggerated reaction at the seat of emotions. Does not depress cortical activity. Does not impair mental efficiency or normal behavior. No risk of drug-induced depression.

RELIEVES ASSOCIATED PHYSICAL TENSION
by relaxing skeletal muscle. Aids restful sleep and reduces likelihood of symptom formation due to depression. Does not impair motor control.

- Confirmed efficacy
- Documented safety
- Simple q.i.d. dosage

▲Deprol▲†

benactyzine + meprobamate

Supplied: Bottles of 50 light-pink, scored tablets.
Composition: Each tablet contains 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

WALLACE LABORATORIES, *New Brunswick, N. J.*

†TRADE-MARK

CD-922Q

NOW—YOU CAN PRESCRIBE THE UNSURPASSED ADVANTAGES OF

superior antiallergic efficacy
with new low dosage

NEW

Arist

- combines the **anti-inflammatory, antiallergic** and **antihistaminic** effects of two agents—ARISTOCORT and chlorpheniramine which, separately, have been proved highly effective in the treatment of allergy
- permits **greater latitude** in adjusting dosage to minimum level needed for maintenance, because ARISTOCORT and chlorpheniramine are supplied in the **lowest dose tablets available** for each component alone
- supplies **ascorbic acid** for increased demand in stress conditions

Indications: *Generalized pruritus of allergic origin; hay fever, allergic rhinitis, perennial asthma, seasonal and perennial rhinitis, vasomotor rhinitis; drug reactions and other allergic conditions.*

Dosage: *One to eight capsules a day in divided doses. Dosages should be established on the basis of individual therapeutic response.*

Precautions: *Drowsiness may occur, and is usually due to the antihistamine effect. Occasionally this may also cause vertigo, pruritus and urticaria. Because of the low dosage, side effects with* ARISTOMIN *have been relatively infrequent and minor in nature. However, since* ARISTOCORT *Triamcinolone is a highly potent glucocorticoid with profound metabolic effect, all precautions and contraindications traditional to corticosteroid therapy should be observed. Discontinuance of therapy must not be sudden after patients have been on steroids for prolonged periods. It must be carried out gradually over a period of as much as several weeks.*

Further information available on request.

Supply: *Each* ARISTOMIN *Capsule contains:*

ARISTOCORT® *Triamcinolone..... 1 mg.*
Chlorpheniramine Maleate..... 2 mg.
Ascorbic Acid.....75 mg.

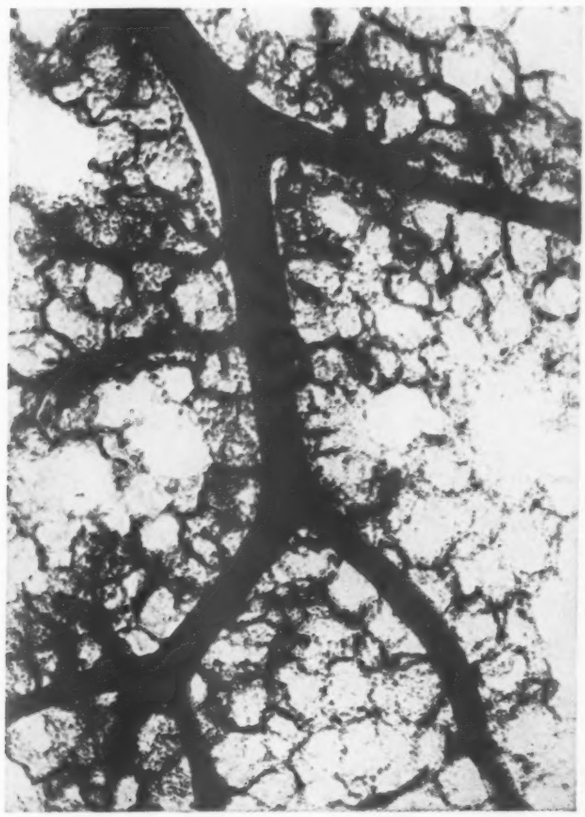
Bottles of 30 and 100

References: *1. Maurer, M. L.: Clinical Report, cited with permission. 2. Levin, L.: Clinical Report, cited with permission. 3. Gaillard, G. E.: Clinical Report, cited with permission.*

ARISTOCORT IN ANTIHISTAMINE COMBINATION

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Steroid-Antihistamine Compound LEDERLE



(lung x 65, injected with carbon-gelatin)

comments by clinical investigators:

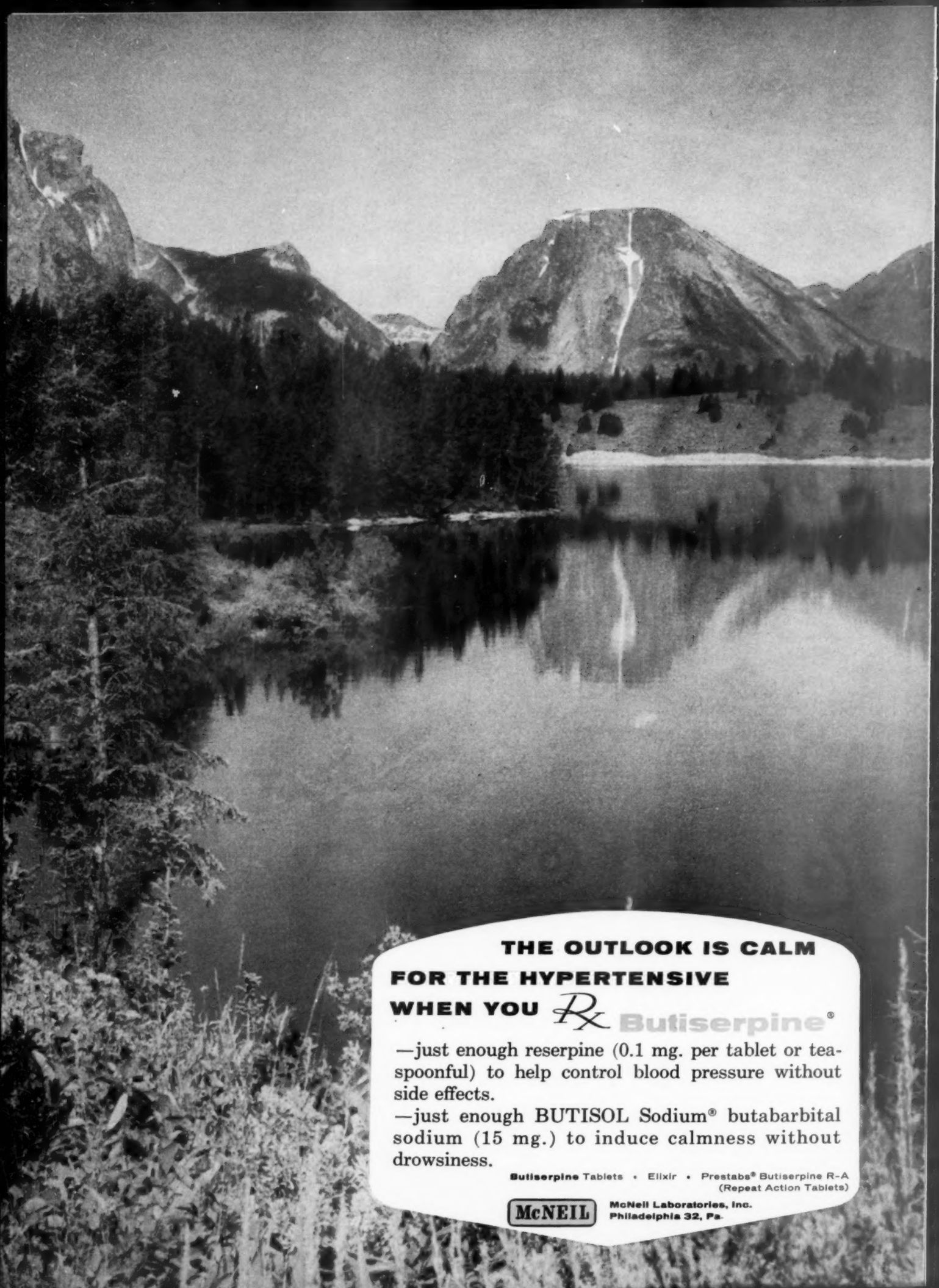
"I would conclude that ARISTOMIN *is truly a worthwhile aid in treating allergic problems."*[1]

"The results have been uniformly good. The patients have stated that their symptoms were very much relieved. I have not encountered any side reactions except from one patient, who complained of some drowsiness, which I attribute to the antihistamine."[2]

"In general . . . it [ARISTOMIN] *is an excellent product. Over-all, it appears to be more effective than any simple antihistamine we have used. Despite the fact that we employed it in the treatment of a variety of nonselected individuals and problems, we had excellent and good results in 25 of the 39 patients."*[3]

Lederle

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y.


THE OUTLOOK IS CALM
FOR THE HYPERTENSIVE
WHEN YOU Rx Butiserpine®
—just enough reserpine (0.1 mg. per tablet or teaspoonful) to help control blood pressure without side effects.
—just enough BUTISOL Sodium® butabarbital sodium (15 mg.) to induce calmness without drowsiness.
Butiserpine Tablets • Elixir • Prestabs® Butiserpine R-A (Repeat Action Tablets)
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the oral antidiabetic most likely to succeed



DIABINESE®

brand of chlorpropamide

The superior effectiveness of DIABINESE increases the chance of success of oral therapy in your diabetic patients. Moreover, in properly regulated dosage, DIABINESE is free from significant incidence of serious side effects. Incidentally, your patients will appreciate the economy possible (savings up to 50%) when DIABINESE is the oral therapy selected.

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when replacement or reduction of insulin is desirable...

"In the majority of cases requiring less than 40 U. insulin daily, chlorpropamide could be substituted with success. However, even in 21 diabetic patients requiring as much as 60 U. of insulin daily, we succeeded in achieving good metabolic equilibrium with chlorpropamide."

Bloch, J., and Lenhardt, A.: Ann. New York Acad. Sc. 74:954, 1959.

when other oral therapy has failed...

"Comparison of diabetic control between tolbutamide and chlorpropamide in the same patients shows that good control often can be achieved with chlorpropamide when tolbutamide has been proved ineffective."

Lee, C. T., Jr.; Schless, G. L., and Duncan, G. G.: Ibid., p. 738

when dietary control proves impractical...

"Oral administration [of chlorpropamide] in therapeutic doses leads to predictable drug levels in the serum... With it a better control can be obtained in that large segment of the diabetic population that does not fully cooperate in the dietary management."

Handelsman, M. B.; Levitt, L., and Calabretta, M. F.: Ibid., p. 632.

the oral antidiabetic most likely to succeed

DIABINESE®

brand of chlorpropamide

economical once-a-day dosage



available as 100 mg. and 250 mg. tablets

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for the tense and nervous patient

relief comes fast and comfortably

–does not produce autonomic side reactions
–does not impair mental efficiency, motor control, or normal behavior.

Usual Dosage: One or two 400 mg. tablets t.i.d.

Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets or as MEPROTABS*–400 mg. *unmarked,* coated tablets.

Miltown®

meprobamate (Wallace)

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CM-8284

In hypoprothrombinemia

KONAKION

Rapid action	rate of absorption faster than menadione or derivatives... more potent and lasting effects.
Wide margin of safety	substantially safer than vitamin-K analogues—no kernicterus reported.
Versatility of administration	capsules for oral use...fine aqueous dispersion for parenteral administration.
Compatibility	unlike vitamin-K analogues or similar products, the parenteral form of Konakion is a fine aqueous dispersion compatible with most I.V. vehicles.
Low dosage forms	no excess, no waste—packaged for economical one-time use.

Prophylactically and therapeutically, Konakion is indicated in obstetrics to prevent or control neonatal hemorrhage, to minimize excessive bleeding in surgery, to offset anticoagulant overdosage, and whenever vitamin-K utilization is impaired.

KONAKION®—brand of vitamin K_1
ROCHE® Capsules—5 mg; Ampuls—1 mg/0.5 cc; 10 mg/1 cc; 25 mg/2.5 cc

STOP BLEEDING

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey

SPONTIN®

(Ristocetin, Abbott)

A STATISTICAL REVIEW* OF THREE HUNDRED THIRTY-THREE CASES

**Records of Medical Department, Abbott Laboratories, North Chicago, Illinois*

SPONTIN (Ristocetin, Abbott) is a new antibiotic discovered and developed at Abbott Laboratories. Its two components, and B, have been isola line state from the fer of a new species of *Nocardia lurida*. Bot are active against gra teria and mycobacte mycete was isolated f ple collected from th Gods, Colorado Sp No other culture wh same antibiotic has

The chemical cha ristocetins are not c though they are kn teric substances con phenolic groups a ristocetin A and ris molecules with m the vicinity of 400 have good stabilit pH range of bloc SPONTIN is a ly tion, derived fr material, represe ristocetins A an

Antimicrobial tion against gra ganisms, SPON effective than able antibiotics

Against pne cocci (except s cocci) the anti tericidal at th concentration hibits the gro also kills the

This obse for the majo lococci. Ho staphyloco have been t centration s minimum i produce a this reaso SPONTIN i for the treat and enterococcal infections.

Cultures of staphylococcus aureus, which are resistant to other antibiotics have been shown to be sensitive to SPONTIN. There has been no case reported in-which a staphylococcal or enterococcal strain has exhibited a

SPONTIN

pH range of blood a SPONTIN is a lyophilized prepara-

tion, derived from pure crystalline material, representing a mixture of ristocetins A and B.

Antimicrobial Properties. In its action against gram-positive coccal or- SPONTIN is notably more tly avail-

d strepto- of entero- riably bac- sage. The which in- organisms

holds true s of staphy- e strains of ococci which quired a con- gher than the centration to effect. It is for her dosage of recommended staphylococcal tions.

coccus aureus, o other antibi- to be sensitive s been no case aphylococcal or has exhibited a SPONTIN.

that the antibi- TIN is enhanced gamma globulin. supported by the *vivo* activity of mes greater than from the *in vitro*

estigators* have re- cal response follow- ration of SPONTIN dies have shown a vity on the part of ganism. Satisfactory may be expected sm requires up to 25 ONTIN for inhibition llowing table shows nsitivities of different he major pathogenic groups.

Summary and Conclusions

Major use has been treating staphylococcic infections. Of the total 333 cases, approximately one-third was treated for pneumonia; of these over 80% were either cured or improved. About 70% of these pneumonias were caused by staphylococci.

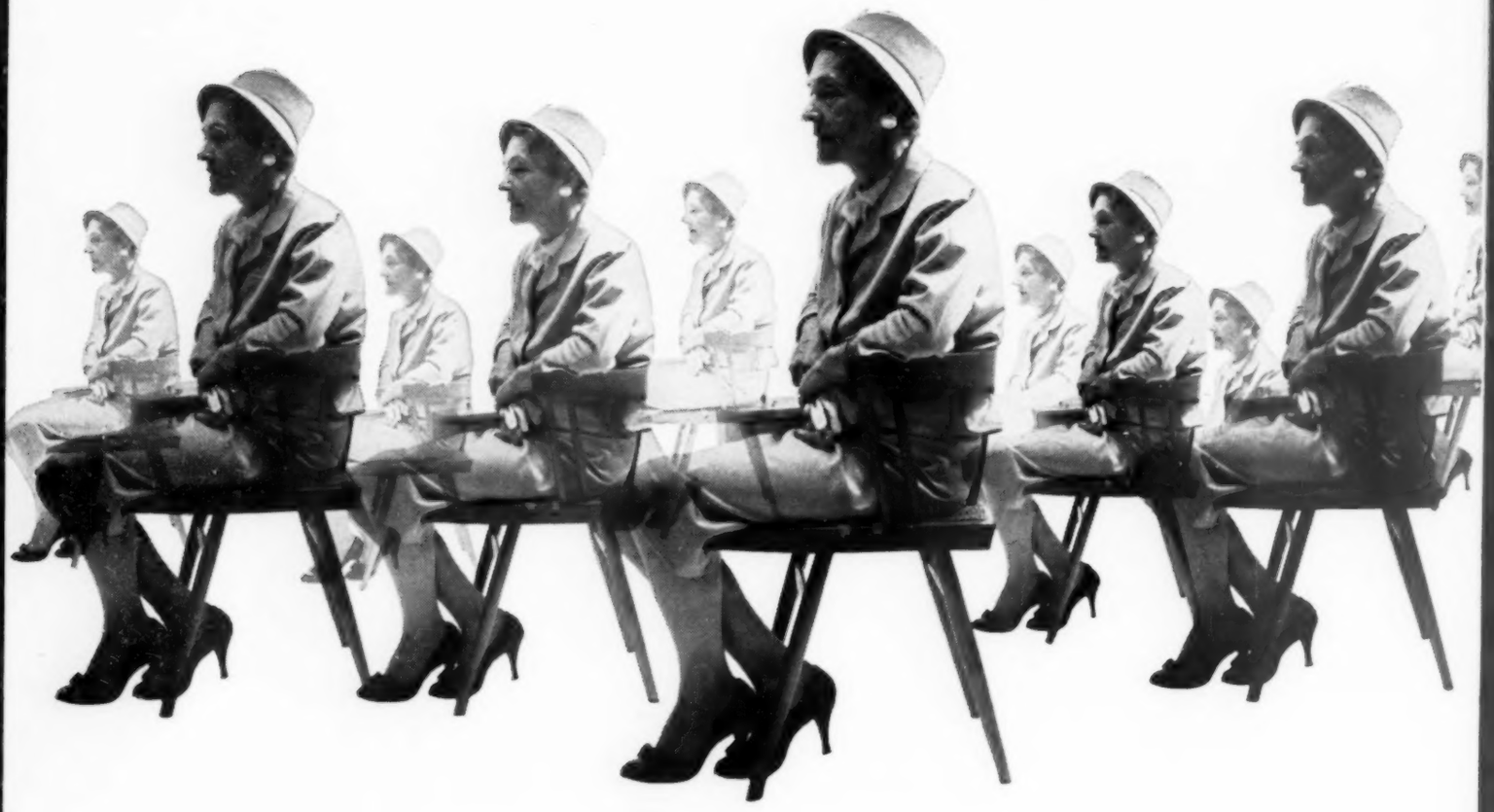
The next largest group included 46 patients with subacute bacterial endocarditis. About 50% of these infections were identified as staphylococcic and a further 15% as enterococcic. Other infections included 38 cases of septicemia, 32 abscesses and 24 patients with osteomyelitis.

The administration of SPONTIN brought about a cure in 60% of all the cases reviewed and improvement in a further 17%.

Side-effects were seldom troublesome when a daily dose of 2 Gm. was not exceeded. The incidence rose as the dosage was increased. The most disturbing side-effect after administration of SPONTIN has been neutropenia. However, in all instances this has responded to either discontinuance of medication or reduction in dose.

908146

How many patients today complained about pain?



non-narcotic—pain relief equivalent to that of codeine

well tolerated in both acute and prolonged use

wide range of indications—general practice and the specialties

analgesia plus anti-inflammatory action

Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid.

remember

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Ethoheptazine Citrate with Acetylsalicylic Acid, Wyeth

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Philadelphia 1, Pa.

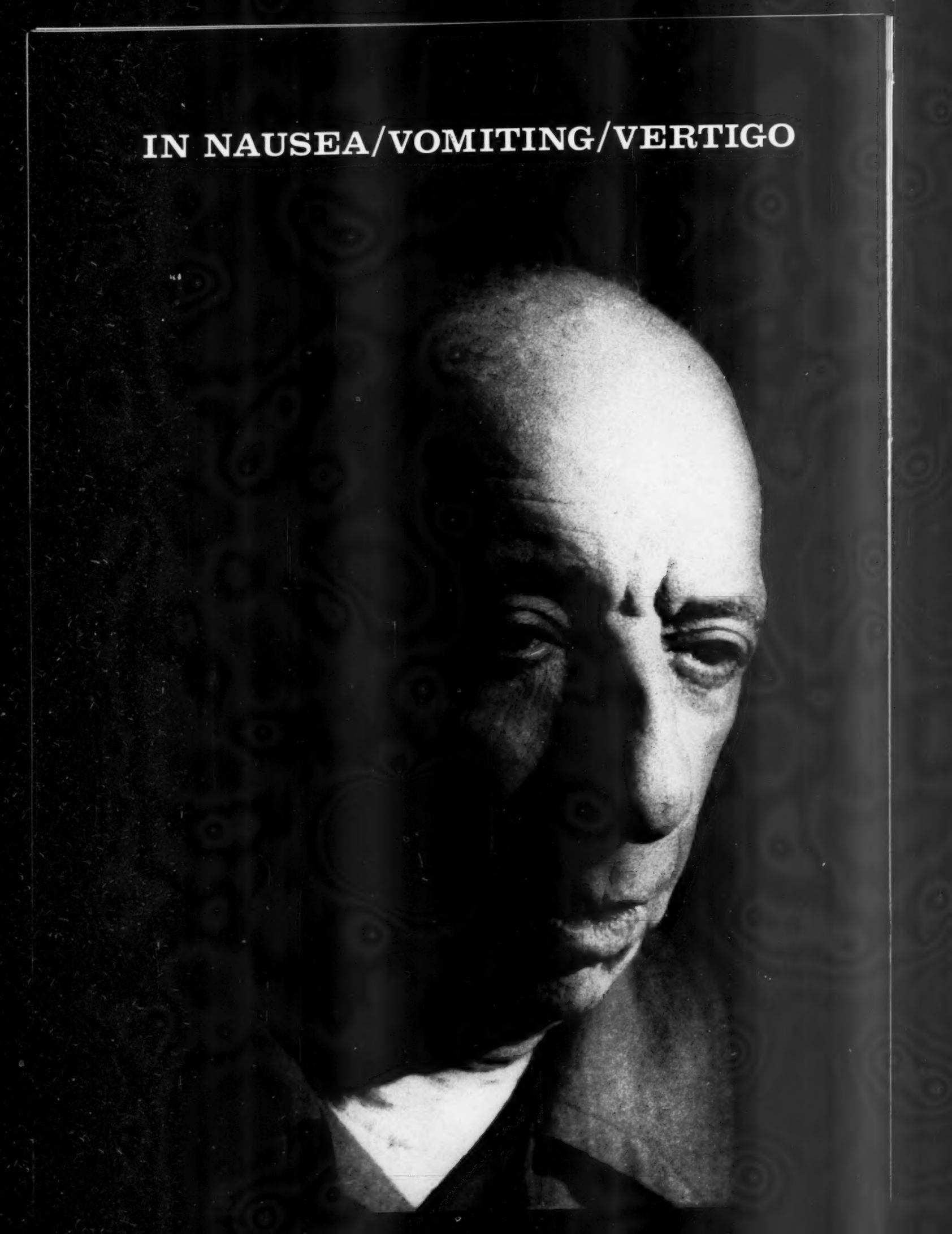


Raudixin–the cornerstone of antihypertensive therapy–helps relieve the pressures in your patients–helps relieve the pressures on your patients / 50 and 100 mg. tablets whole root rauwolfia for exceptional patient response

SQUIBB Squibb Quality—the Priceless Ingredient

Squibb Whole Root Rauwolfia Serpentina/'RAUDIXIN'® IS A SQUIBB TRADEMARK

IN NAUSEA/VOMITING/VERTIGO



USE

SPECIFIC
Avoids unnecessarily diffuse or diverse drug action; effective in economical once-a-day dosage

ESTABLISHED
6-year record of successful use in daily practice; consistently favorable reports[1-10]

UNCOMPLICATED
Has no known contraindications; free of hepatic, hypotensive, and hematologic hazards observed with phenothiazines

BONAMINE*

brand of meclizine hydrochloride

SUPPLIED:

BONINE Tablets, scored, 25 mg.

BONINE Chewing Tablets, mint-flavored, 25 mg.

BONINE Elixir, cherry-flavored, ideal for children, 12.5 mg. per teaspoonful (5 cc.).

DOSAGE: Adults, 25 to 50 mg. once a day. Children, usually half the adult dose.

BONINE REFERENCES:

1. Moyer, J. H.: M. Clin. North America, Mar., 1957, p. 405.
2. Seidner, H. M.: Illinois M. J. 109:20, 1
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10. [illegible] by Army, Navy, Air Force Motion Sic[illegible] A.M.A. 160:755, 1956.

INDICATIONS:

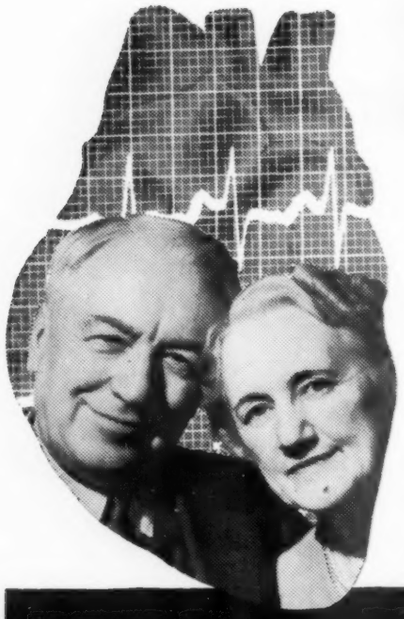
Including nausea and vomiting of pregnancy • motion sickness • radiation sickness • vertigo associated with cerebral arteriosclerosis



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2 *exclusive advantages in quinidine therapy*[1,2] *to control* **cardiac arrhythmias**

QUINAGLUTE®
DURA-TAB S.M.®

the only oral Sustained Medication* Quinidine Gluconate (5 gr.)

b.i.d. dosage (every 12 hours)

Each dose of **Quinaglute Dura-Tab S.M.** maintains uniform plasma levels up to 12 hours.
No night dosage needed.
No valleys where arrhythmias tend to recur.[1]

a well tolerated quinidine

Only **Quinaglute Dura-Tab S.M.** provides quinidine gluconate for oral use. Ten times as soluble as quinidine sulfate, the gluconate is better tolerated by the gastrointestinal tract.

An unexcelled quinidine in premature contractions auricular tachycardia flutter, fibrillation

REFER TO PDR PAGE 867

Dosage: for **conversion** of auricular fibrillation to normal sinus rhythm, in most cases, 2 Quinaglute Dura-Tab S.M. tablets 3 to 4 times a day, for 2 to 3 days; longer periods are required in some patients . . . for **maintenance** 1 to 2 tablets every 10 to 12 hours. Bottles of 30, 100 and 250.

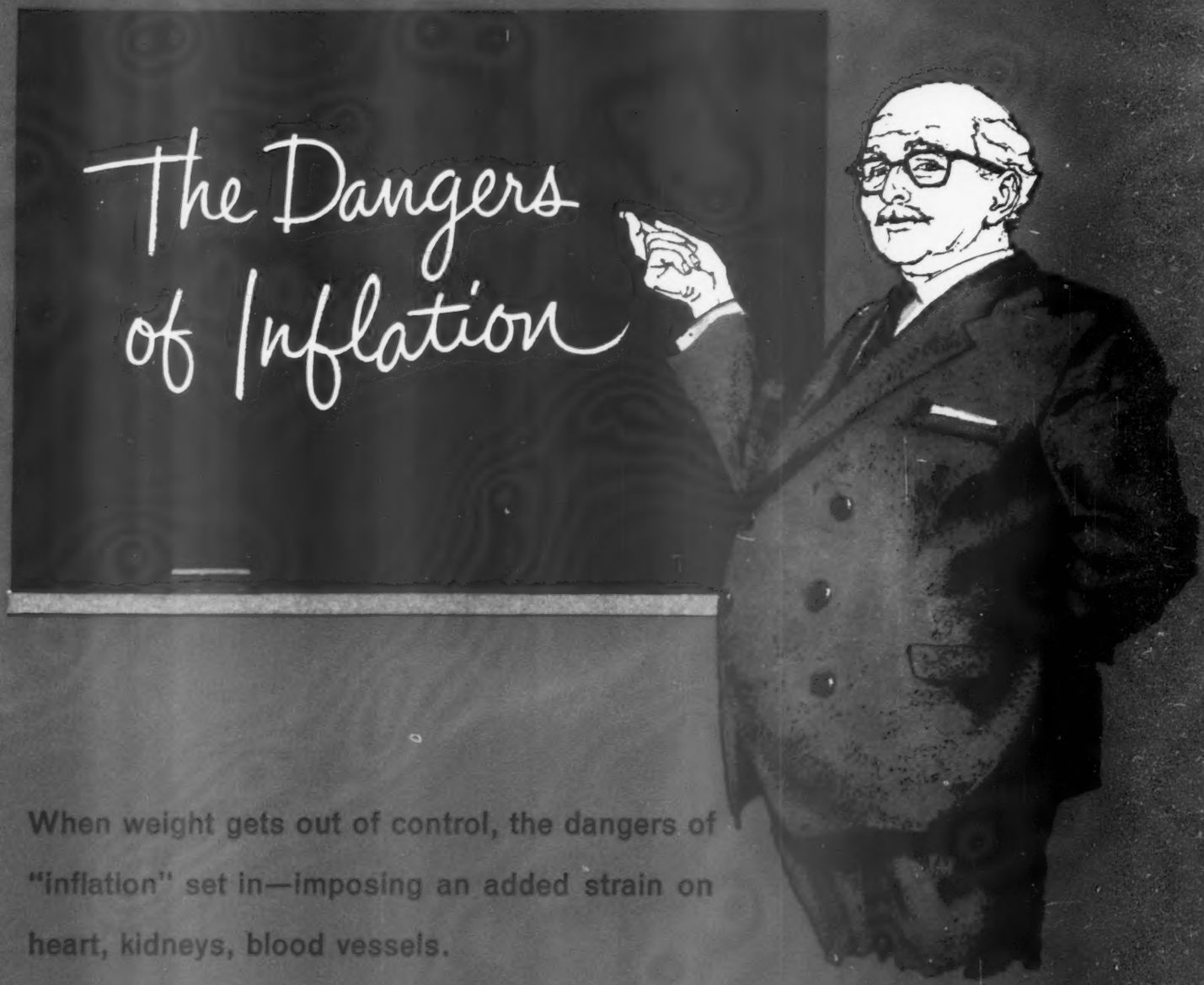
1. Bellet, S.: Finkelstein, D., and Gilmore, H.: A.M.A. Archives Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.

Samples and complete literature available from **WYNN PHARMACAL** CORPORATION
5119 West Stiles Street, Philadelphia 31, Pa.

Now also available...INJECTABLE QUINAGLUTE
10 cc. Multiple Dose Vials, 0.08 Gm. Quinidine Gluconate per cc.

* U. S. PATENT 2,895,881

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When weight gets out of control, the dangers of "inflation" set in—imposing an added strain on heart, kidneys, blood vessels.

Keep your obese patient on his diet...

SYNDROX®

methamphetamine hydrochloride

—curbs the desire for food, at the same time combats depression that may accompany dieting. The result is less interest in eating, more interest in other activities.

SYNDROX TABLETS 5 mg.
ELIXIR 5 mg. per 5 cc.

Dosage: ½ to 1 tablet or teaspoonful two or three times a day ½ to 1 hour before meals.

McNEIL

McNeil Laboratories, Inc.
Philadelphia 32, Pa.

Unquestioned therapeutically

...long established clinically

TRISEM

SUSPENSION (chocolate-flavored)

For the many bacterial infections that respond promptly to triple sulfonamide therapy, Trisem presents a preferred formula.

Each 5 cc. contains, in a pleasant, chocolate-flavored vehicle:

Sulfamerazine (microcrystalline)	0.167 Gm. (2 3/5 gr.)
Sulfadiazine (microcrystalline)	0.167 Gm. (2 3/5 gr.)
Sulfamethazine (microcrystalline)	0.167 Gm. (2 3/5 gr.)

Each 5 cc. (1 tsp.) provides 0.5 Gm. total sulfonamides.

Each 15 cc. (1 tbsp.) provides 1.5 Gm. total sulfonamides.

ADVANTAGES

- **wide patient acceptability**
- **unquestioned therapeutic value**
- **high index of safety**
- **broad antibacterial spectrum**
- **provides high blood levels promptly**
- **economical for the patient**

Many physicians prefer to use the sulfonamides to control bacterial infections because resistant organisms rarely develop. Nor, as with some broad spectrum therapy, is there the complication of such after-effects as moniliasis.

PACKAGING: In pint and gallon bottles.

THE S. E. MASSENGILL COMPANY

BRISTOL, TENNESSEE

New York Kansas City San Francisco

safely control the "target symptoms" of emotional stress with the smallest effective dosage (0.25 mg. b.i.d.) of any neuroleptic* agent



the promise of

PERMITIL®

Fluphenazine dihydrochloride

in everyday office practice



Primer on PERMITIL

Q. Why another psychopharmacologic agent?

A. The ever-expanding role of chemistry in the treatment of mental and emotional problems in this new era of psychopharmacologic drugs is amply attested to by the growing number of rauwolfia, mephenesin, diphenylmethane and phenothiazine derivatives now in clinical use. When one considers the wide range of indications to be treated—from severe psychosis to mild situational stress—it becomes somewhat clearer as to the reason for the number and diversity of drugs available. In addition, improvements and refinements of existing agents are constantly taking place. Drugs tailored to perform a selected, single function are emerging. So it is with PERMITIL.

Q. Why another phenothiazine?

A. All members of this group contain a phenothiazine nucleus and a side chain attached to the nitrogen atom. Differences in potency are related to specific chemical alterations in these compounds. Clinical evidence demonstrates that the phenothiazines act principally, but to varying degrees, on several subcortical areas of the brain. Thus, certain of these drugs produce sedation and potentiate the action of barbiturates, while others do not; autonomic side effects (such as blurred vision, constipation) are produced by some and not by others; some have been shown to be very effective antiemetic agents. At certain dosage levels, the phenothiazine derivatives also may cause extrapyramidal side effects. These, however, are neuropharmacologic rather than toxic effects and are totally reversible.

Since there is a correlation between the dosage of a phenothiazine derivative and the frequency and the type of side effects it causes, ***the less of the drug needed to achieve therapeutic results, the less likely are serious side effects.*** **Thus, the lower the effective dosage of a phenothiazine derivative, the lower the incidence of unwanted side reactions and, conversely, the higher the level of therapeutic response.**

For these reasons, the search has been unceasing to develop a phenothiazine with an optimum therapeutic ratio.

Q. What is a "neuroleptic" agent?

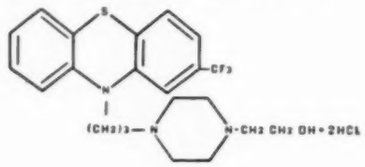
A. The term "neuroleptic" implies a specific effect of a pharmacologic agent on the nervous system. It refers to a mode of action on specific subcortical areas which strongly influence emotional behavior in contradistinction to hypnotic agents which dull the senses. Neuroleptics achieve control of anxiety symptoms without inducing either somnolence or euphoria. Thus, there is an increase in the patient's capacity to cope with life's problems more successfully. The terms "tranquilizers" and "ataraxics" are descriptively impressive, but they fail to convey what seems pharmacologically unique.

Q. Why introduce the term "neuroleptic"?

A. Because it has a precise psychopharmacologic meaning and is more descriptive of the action of PERMITIL than any other current term.

Q. What is PERMITIL?

A. PERMITIL is a new anti-anxiety agent of extraordinary potency and effectiveness. Chemically, PERMITIL is 1-(2-hydroxyethyl)-4-[3-(2-trifluoromethyl-10-phenothiazinyl)-propyl]-piperazine dihydrochloride. The structural formula is:

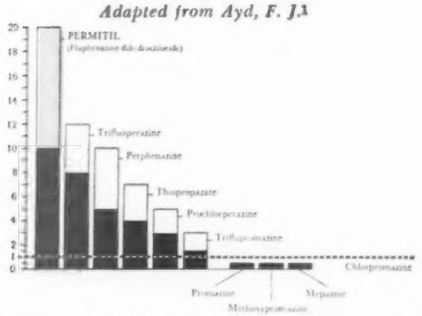


Q. Why is PERMITIL unique?

A. Although PERMITIL can be broadly classified as a phenothiazine, it exhibits a spectrum of unique effects at unprecedented low dosage—a feature that markedly distinguishes this compound from other anti-anxiety drugs.

The Relative Therapeutic Potency of Various Phenothiazines

Adapted from Ayd, F. J.[1]



The potency of each drug was determined by the criteria proposed by Freyhan.[2] These were: *(1)* the attainable level of psychomotor inhibition, *(2)* the speed of action, and *(3)* the dosage required to obtain effective action.

Q. What are the distinctive clinical advantages of PERMITIL?

A. Extensive clinical studies have established important psychopharmacologic advantages for PERMITIL.

1. The effective dosage of PERMITIL *(0.25 mg.* b.i.d.) is the lowest safe dosage of any antianxiety agent. Since fractional milligram doses of PERMITIL usually produce a therapeutic effect, many of the annoying side effects of the other phenothiazines, which are dose-related, occur less frequently or not at all. In fact, any side effects associated with dosage not exceeding 1 mg. per day have been uncommon and transitory. PERMITIL represents an advance over its predecessors[1] because of its higher level of therapeutic response and low order of side reactions.

2. Unlike other phenothiazines, PERMITIL alleviates symptoms of anxiety, tension, agitation and emotional unrest *without* depressant effect, impaired alertness or slowed intellectual function. Furthermore, anxiety-induced symptoms of apathy, indifference, listlessness, reduced initiative and chronic emotional fatigue (often refractory to other phenothiazines) frequently respond to administration of PERMITIL. Thus, a significantly wider spectrum of "target symptoms" amenable to therapy is an outstanding property of PERMITIL.

3. Onset of action is rapid and patients soon become more relaxed and less tense. The patient regains a more confident outlook and normal drive is restored.

4. PERMITIL has an inherently long duration of effect. This makes possible a particularly convenient and easy-to-remember schedule of morning and evening dosage.

Q. For what, specifically, is PERMITIL indicated?

A. PERMITIL is indicated for the control of the "target symptoms" of emotional stress so common in everyday office practice. The basic areas of usefulness for PERMITIL are: (1) behavioral disturbances characterized by anxiety, tension, apprehension and instability, as well as depressive symptoms associated with anxiety states; (2) emotional stress accompanying organic disorders and complicating recovery from, or acceptance of, the underlying condition; (3) chronic disorders in which anxiety and stress are contributing factors, e.g., gastrointestinal dysfunctions, neurodermatitis, asthma, premenstrual tension, arthritis, hypertension and tension headache.

Q. Is the dosage schedule, as with many phenothiazine derivatives, complex and complicated?

A. No. PERMITIL has an inherently long duration of effect so that twice-a-day dosage provides the patient with day and night symptom alleviation. The lowest dose of PERMITIL that will produce the desired clinical effect should be used. *The recommended dose for most adults is one 0.25 mg. tablet twice a day.* This may be increased to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms who have had a trial of lower dosages first that were well tolerated but were only partially effective. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. (Dosage for children has not been established.)

Q. What about side effects and contraindications to PERMITIL?

A. At the recommended dosage of PERMITIL, side effects have been observed infrequently or not at all. PERMITIL, as with other phenothiazines, is contraindicated in severely depressed states.

Q. How is PERMITIL supplied?

A. PERMITIL is available as Tablets, 0.25 mg., bottles of 50 and 500.

References: 1. Ayd, F. J.: The current status of major tranquilizers, in press. 2. Freyhan, F. A.: Therapeutic implications of differential effects of new phenothiazine compounds, Am. J. Psychiat. 115:577-585 (Jan.), 1959.

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1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.



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Editorial

Systemic Lupus Erythematosus—Disease of an Unusual Immunologic Responsiveness?

THE suggestion has often been made that a form of anaphylactic hypersensitivity is involved in the pathogenesis of systemic lupus erythematosus (SLE). This suggestion arose primarily from certain similarities between the symptoms and pathologic lesions of SLE and serum sickness, and from the experiments of Rich in which vascular lesions were induced by experimental anaphylactic reactions. However, supporting evidence derived from study of the immune reactions of the patients has been lacking.

Recently it has been possible to characterize many abnormal serologic reactions which occur in this disease. Evidence suggesting the existence of an autoimmunity has been obtained. The results strengthen the view that an abnormal immunological response is present in SLE, but indicate that the abnormality may be a type which has not been previously recognized.

The number of autologous tissue components to which circulating antibodies can be found in SLE is striking. γ-globulins which react with the red blood cells occur frequently [*1*]. Leucagglutinins arise in patients with SLE without prior transfusions [*2*]. Platelet agglutinins may play a role in the occasional thrombocytopenic purpura [*3*]. A γ-globulin circulates which has an antithromboplastic activity [*4*], and another is commonly present which gives rise to a false positive Wassermann reaction [*1*]. Seemingly large amounts of γ-globulin are present in the renal lesions [*5*] and in the fibrotic lesions of the spleen [*6*].

The discovery of the L.E. cell by Hargraves has led to identification of a group of serum factors which react with different constituents of the cell nucleus [*7*]. The L.E. cell appears to result from the interaction of one such factor with nuclear nucleoprotein, for which both DNA and histone are essential. Separate factors are present which react with pure DNA, isolated histone, and with an unidentified substance extractable from the nucleus with isotonic buffers [*8*]. One or more γ-globulins may arise which react with cytoplasmic constituents [*9*]. The antinuclear factors are noteworthy because of the known poor experimental antigenicity of nucleic acids and histone.

The evidence that these reactions are immunological is reasonably good in all cases and very good in a few. All the serum factors are γ-globulins. Most of the reactions have been shown either by identification of the γ-globulin on the affected cell or tissue, or by such immunological technics as complement fixation, precipitation, hemagglutination or passive cutaneous anaphylaxis. The L.E. cell factor and the factor which precipitates with DNA have been recovered in purified form from combinations with nucleoprotein and DNA, respectively. They possess the physical and immunological characteristics of typical human antibody γ-globulin. The capacity of these factors to react with the patient's own cell materials suggests that they are autoantibodies.

Evidence for hyper-reactivity to foreign antigens in SLE has also appeared. Patients with

SLE have been found to be among the most prolific producers of antibodies to rare blood group substances [*10,11*]. They have been reported to produce demonstrable antibodies to antibiotics more frequently than most other patients [*12*]. However, hyper-reactivity to foreign antigens remains to be established by quantitative, comparative studies with standardized antigens.

There is thus considerable evidence that unusual antibodies, including autoantibodies, arise in SLE. The circumstances leading to their appearance are obscure. A spontaneous alteration in the patient's cells rendering them autoantigenic would seem unlikely because it would require nearly simultaneous changes in the constituents of many different types of cells. An infectious agent might induce such alterations, for instance in a manner analogous to the alteration of bacterial cell composition and antigenicity by bacteriophage [*13*]. However, neither altered cell constituents nor infectious agents have been identified in SLE. The ready reactivity of the serum factors with cell components from normal human and animal tissues argues against a primary change in cell antigenicity, but is not conclusive because antibodies to abnormal cells can cross react with normal cells. Thus the hypothesis that an altered cell antigenicity exists in SLE has not been excluded, but supporting evidence has not yet appeared.

On the other hand, the multiplicity of cell components to which antibodies are formed, the varying patterns appearing in different serums, and the probable hyper-reactivity to foreign antigens suggest that an unusually productive antibody synthesizing system is present. In this instance, an abnormal immune system would be reacting against normal cell constituents.

What is the role of the serum factors in the pathogenesis of the disease? Certainly in some instances, they may be responsible for a hemolytic anemia or a thrombocytopenic purpura. However, some of the factors are present more often than is a corresponding clinical syndrome, and these syndromes themselves are not essential features of the disease. Considerable evidence is accumulating that the antinuclear antibodies, which are capable of reacting with the nucleus of most cells, cannot gain access to the nucleus of a normal cell. Thus it appears that the mere presence of these factors is not usually sufficient to induce tissue lesions. Furthermore, the disease can occur without any of the known serum factors being demonstrable, indicating that they are not essential in pathogenesis.

It remains possible that the serum factors require some preliminary tissue injury before they can alter cells *in vivo*. Antigen-antibody complexes involving one or more serum factors may arise during the normal disintegration of cells and they may be injurious. It may be that current technics are inadequate to demonstrate these or other ways in which the factors are pathogenic. However, the evidence to date supports the view that the factors are by-products of a deranged immune system rather than decisively important pathogenic agents.

The possibility therefore arises that the deranged system is responsible for the disease in some other way. This implies existence of an immunologic aberration which can induce autologous tissue injury and also give rise to a variety of autoantibodies. Currently recognized types of hypersensitivity have not yet been shown to possess this capacity. Thus understanding of the abnormality is likely to require a search for new types of immunologic reactions. In recent years there have been important additions to the group of biological reactions which appear to have an immunological basis. Any one of these might conceivably provide the clue to an understanding of the abnormality in SLE.

Immunologic tolerance has been discovered [*14*]. In this phenomenon, exposure of a fetus to an antigen will prevent that individual, upon reaching adulthood, from reacting to that antigen. By inference, normal people may not form autoantibodies because they are "exposed" to their own cells *in utero*, and thus become tolerant.

After establishment of a state of tolerance, or after paralysis of the immune response by radiation, it has been possible to populate one animal with functional bone marrow or spleen cells of another of the same or different species. A characteristic disease often results which is apparently the result of an immune reaction of the graft against the host [*15*]. Thus, at least under these unusual circumstances, one type of viable cells within an individual can react immunologically against another type, with deleterious consequences.

Less clearly immunological but potentially quite significant are the observations of biologists

on the capacity of cells to recognize and react with one another [*16*]. Isolated cells in suspension can recombine to form tissues similar to those of their origin. In doing so, they will avoid or reject cells of unlike origin. Mixtures of cells will segregate themselves according to tissues or origin. The mechanism of this behavior remains obscure; for example, it is not known whether materials secreted by the cells contribute to their compatibility or incompatibility. It is conceivable that these reactions between cells are a more general expression of the function of antibody production which is a specialized activity of the lymphatic system.

Exploration of the tissues and immune systems of patients with SLE for aberrations in reactions such as these may prove fruitful. Abnormalities in the behavior of one cell or tissue toward another in cell suspensions may be demonstrable. Abnormal tolerance mechanisms may be found, in which the patient loses "tolerance" of his own cells. Perhaps cells with different somatic or genetic composition exist in the patients and react against other cells or cell products with which they normally would be compatible. This latter idea is made less unreasonable by two recent findings. The first is the observation that within certain inbred strains of mice, homografting of skin is possible in all combinations except from male to female [*17*]. This suggests that tissue incompatibilities can exist which bear some relationship to the chromosome composition of the cells. The second is the demonstration of chromosome differences in certain human diseases [*18*], and the probable identification of the first human genetic mosaic [*19*].

An excellent example of the application of some of these concepts to a supposedly autoimmune disease has been provided by Paterson [*20*]. He has succeeded in transferring experimental allergic encephalomyelitis from one rat to another by means of washed lymph node cells. To accomplish this, it was necessary to make the recipient rat tolerant of the donor cells by neonatal injection of spleen cells from the prospective donor. The donor cells when administered later, after the recipient had matured, could then survive long enough to induce the disease. This induction of the disease presumably has an immunological basis but the precise mechanism remains to be clarified.

One significant aspect of this work is the lead it provides toward achievement of an experimental model of SLE and related diseases. A way may be found to transfer an abnormal immunologic response from man to a tolerant animal. This latter development would be facilitated if a delayed or cellular hypersensitivity to autologous tissue existed in SLE. While no clear evidence for such a phenomenon has appeared, some suggestive data are accumulating. Intradermal injection of autologous leukocyte homogenates into patients with SLE has led to a skin reaction consisting of erythema, induration and inflammatory cell infiltration beginning at about ten hours and lasting until thirty-six hours [*21*]. The reaction is independent of disease activity and also of the presence of serum antibodies capable of reacting with cell constituents. Similar reactions have not occurred to any extent in normal subjects, but considerable work remains to be carried out before this reaction can be adjudged an autoimmune reaction of a delayed type.

Another useful approach may lie in exploration of the relations between rheumatoid arthritis and SLE, and the genetic backgrounds of patients with these illnesses. The clinical similarities of the two, despite obvious differences, has long been recognized. However, the hallmark of rheumatoid arthritis has been the rheumatoid factor which is a γ-globulin of high molecular weight, and probably is a peculiar type of antibody. The hallmark of SLE has been the L.E. cell and what now appears to be a group of antinuclear antibodies. The coexistence of these two types of unusual γ-globulins in the same person is known. It now appears that relatives, often asymptomatic, of patients with classic SLE may have the rheumatoid factor in their serum [*22*]. This suggests a familial predisposition to an abnormal immune response which in some instances may manifest itself as rheumatoid arthritis, sometimes as SLE, and sometimes as serologic reactions without clinical symptoms.

These suggestions are highly speculative, and may hold little merit in themselves. However, although classic immunologic technics have provided strong evidence for an abnormality of the immunologic response in SLE, considerable doubt remains about the importance of the specific reactions identified in the initiation of the disease. If these reactions are now studied in the context of newer knowledge of immunologic responses and of the reactions of cells

and tissues to one another, hitherto unappreciated immunologic phenomena may be uncovered which lie closer to the roots of this disease.

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Clinical Studies

Studies on Respiratory Mechanics and the Work of Breathing in Pulmonary Fibrosis*

JOHN R. WEST, M.D.† *and* JAMES K. ALEXANDER, M.D.
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SIGNIFICANT alteration in the physical properties of the lungs as a result of chronic infiltration or fibrosis was clearly indicated by the investigations of Buytendijk [*1*] in 1949. His measurements of pulmonary pressure-volume relationships in three patients with sarcoidosis and in one patient with scleroderma showed considerable stiffening of the lungs involved by these pathologic processes. Similar but lesser alteration in pulmonary pressure-volume relationships was also demonstrated in three of six patients with silicosis. More recently, Lyons [*2*] has reported reduced pulmonary compliance in granulomatous disease of the lung, primarily sarcoidosis.

The purpose of the present study is to investigate further certain alterations in the mechanics of respiration associated with pulmonary infiltrative or fibrotic change of various etiology, insofar as possible relating these alterations to the work required for ventilation of the lung. The term pulmonary fibrosis will be used hereafter to designate a diffuse type of fibrotic or granulomatous alteration of the lung, which involves alveolar capillary septums and also interstitial tissues at a wider plane in relation to bronchi and bronchioles, as well as to branches of pulmonary and bronchial arteries and veins.

In the selection of patients for study, three criteria were considered. Those patients were chosen in whom (1) relative stability of clinical status obtained, (2) the clinical diagnosis was reasonably well established by the usual procedures, and (3) the physiologic defects relative to ventilation, gas exchange, and lung volume were well defined by ancillary pulmonary function tests. The disease process was of at least moderate severity from the clinical standpoint in every instance. As indicated in Table I, etiological diagnoses were varied, including sarcoidosis, asbestosis, silicosis, berylliosis, and probable radiation fibrosis, with three cases of idiopathic disease. There was also some inhomogeneity from the functional point of view. Although the patients with one possible exception (G. R.) were characterized by the presence of alveolar capillary diffusion block, a few were found to have in addition defective intrapulmonary gas

TABLE I
COMPLIANCE OF THE LUNG AND INTRAESOPHAGEAL PRESSURE RELATIVE TO ATMOSPHERE AT THE END-EXPIRATORY POSITION IN NINE PATIENTS WITH PULMONARY FIBROSIS*

Case No.	Patient	Etiological Diagnosis	Compliance (L./cm. H_2O)	P_{IE}-P_B End-Expiratory (cm. H_2O)
I	G. R.	Asbestosis	0.133	0
II	A. S.	Unknown	0.069	0
III	D. F.	Sarcoidosis	0.063	0
IV	H. S.	Radiation	0.056	0
V	I. E.	Berylliosis	0.052	0
VI	E. S.	Sarcoidosis	0.046	0
VII	L. K.	Silicosis	0.039	−1.4
VIII	F. S.	Unknown	0.035	−1.3
IX	G. M.	Unknown	0.019	0

NOTE: Average normal value P_{IE}-P_B End-Expiration = −2.5 cm. H_2O.

* The values for lung compliance were taken as those obtaining over the range of the tidal volume. P_{IE}-P_B End-Expiration refers to intraesophageal pressure relative to atmospheric pressure at the end-expiratory position in centimeters of water.

* From the Cardiopulmonary Laboratory, Presbyterian Hospital, and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York.
† Dr. West died on June 29, 1954.

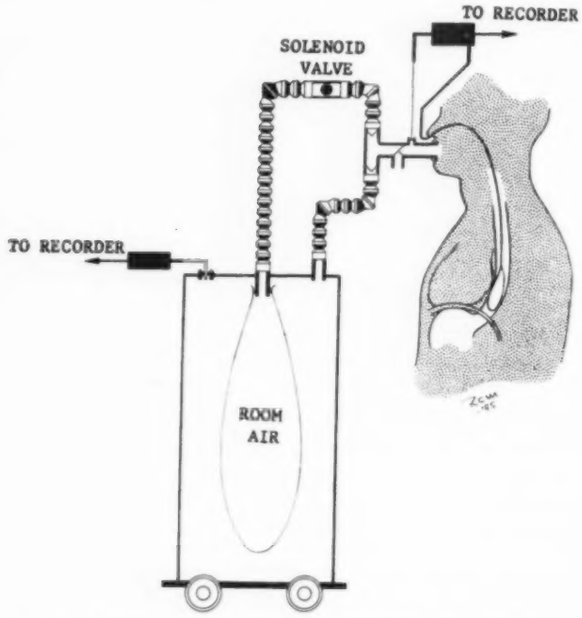


FIG. 1. Apparatus utilized for determination of pulmonary pressure volume loops. See text.

mixing or airway obstruction to varying degree. A brief summary of the clinical findings and course in each case of pulmonary fibrosis appears in the Appendix, and representative roentgenograms of the chest are shown. In two cases (Case IV, H. S., radiation pneumonitis and fibrosis; and Case VI, E. S., Boeck's sarcoid) in which clinical improvement was experienced during the course of steroid therapy, additional data on the function and mechanics of the lung are presented in the Appendix.

METHODS

Six normal subjects and nine patients with pulmonary fibrosis were studied. After anesthetization of the nasal mucous membrane and pharynx with a local spray medication (2 per cent butyn sulfate), a rubber balloon at the end of a polyethylene tube was introduced through the nose into the lower third of the esophagus, so that the distal end of the balloon rested approximately 40 cm. from the nares. The balloon itself measured 16.5 cm. in length with a diameter of 1.0 cm. when collapsed. Multiple small apertures in the wall of the polyethylene tube within the balloon for its entire length insured transmission of a representative intraballoon pressure to the lumen of the polyethylene tube. The tube was thin-walled but inelastic, with an inner diameter of 1.5 mm. and an over-all length of approximately 60 cm. The balloon was completely collapsed within the esophagus by suction on the end of the polyethylene tube, and 1 to 2 ml. of air were introduced before recording pressures.

For measurement of intraesophageal pressure relative to atmosphere the polyethylene tube was connected to a differential strain gauge pressure transducer* with one side of its diaphragm open to atmosphere. The electrical output of the transducer was then carried to an amplifier, oscilloscope and recorder.† A simultaneous recording of the rate of respiratory airflow by means of a Silverman type pneumotachometer and strain gauge pick up, facilitated location of the end-expiratory positions in time on the intraesophageal pressure tracing.

A comparison of the various methods available for estimation of changes in intraesophageal pressure, and detailed consideration of the validity of intraesophageal pressure as an index of mean intrathoracic pressure, are beyond the scope of this discussion. However, it may be noted that the use of the balloon technic for the monitoring of changes in intraesophageal pressure in this study is essentially the same as that previously described elsewhere [*3,4*]. Evidence has been presented that pressure values obtained in this manner are representative of extraesophageal thoracic pressure values [*3*].

The apparatus utilized for determination of pulmonary pressure volume loops is shown in Figure 1. For instantaneous measurement of changes in lung volume, a large thin-walled neoprene bag was suspended in an air tight metal drum of 66 gallon capacity. The inspiratory sidearm of a two way low resistance respiratory valve was connected to the mouth of the bag, and the expiratory sidearm to the air space surrounding the bag within the drum. Thus inspiration by the subject was accompanied by a drop in pressure within the drum, and expiration by a rise toward the preinspiratory pressure level. Relative constancy of the pressure within the drum at the end-expiratory position with successive breaths was chiefly dependent upon maintenance of the same midposition of the chest by the subject, although a very small progressive diminution in pressure within the drum necessarily occurred as a function of the respiratory exchange ratio. Determination of the pressure volume calibration curve of the drum under ambient conditions yielded the expected linear relationship.‡ Changes in lung volume have been reported at

* Model P 23 A. Statham Laboratories, Los Angeles, California.

† Research Recorder, Electronics for Medicine, Inc., White Plains, New York.

‡ An error of up to 40 per cent in estimated changes in lung volume might have been introduced if expansion and contraction of the gas in the drum at the time of calibration had been carried out under isothermal conditions, while the conditions of pressure volume change during spontaneous respiration were more nearly adiabatic. However, the empirical calibration factor was determined under conditions similar to those of spontaneous respiration, and actually differed by less than 10 per cent from the theoretical value expected with adiabatic expansion and contraction.

ambient temperature and pressure as read from the calibration curve of the drum without attempting to correct for the change in temperature and water vapor pressure of expired air considered negligible for purposes of this study. Pressure changes in the drum relative to atmosphere were measured by strain gauge and recorder. Response of this volume recording system to a square wave of pressure delivered at the mouthpiece was complete in less than .02 second. Simultaneous measurement of the pressure differential across the lung was accomplished by connecting one side of a differential strain gauge to the intraesophageal balloon tube and the other to a pressure tap at the mouthpiece. With 1 to 2 ml. of air within it, the response of the balloon and tubing system to a square wave of pressure was complete within .01 second. The output of the strain gauge monitoring changes in pressure within the drum and hence changes in lung volume was placed on the ordinate of an oscilloscopic tracing, and the intraesophageal pressure strain gauge output on the abscissa simultaneously. A long persistence screen permitted photography of the resultant pressure volume loop corresponding to each individual breath. This filmed loop was then projected by means of a photographic enlarger and traced on graph paper.

Data for determination of the static pulmonary compliance (static pressure volume relationship expressed as liters of lung volume change per centimeter of water pressure differential across the lung) were obtained in normal subjects using an interrupter technic similar to that described by Stead, Fry and Ebert [*5*]. A solenoid valve on the inspiratory side of the breathing circuit permitted instantaneous interruption of airflow from three to five times during inspiration from the end-expiratory position to the position of maximum lung volume. A simultaneous recording of changes in volume and pressure differential across the lung at the instant of zero flow permitted construction of the pulmonary compliance curve. Because of reduction in vital capacity this procedure was not usually feasible for determination of lung compliance in patients with fibrosis. In most instances this was accomplished by a simultaneous pneumotachographic and intraesophageal pressure tracing while the subject executed slow respirations of increasing depth over the range of the vital capacity. In each case it was possible for the patient to execute a short respiratory pause with open glottis at the peak of inspiration, so that the compliance values obtained represent static pulmonary compliance data, and may be considered comparable to those obtained in normal subjects by the interrupter technic. Planimetric integration of the pneumotachographic tracing yielded inspiratory volume change of the lung, and the points of zero airflow at end-expiration and end-inspiration on the intraesophageal pressure tracing were readily identified from the pneumotachogram. Construction of the lung compliance curves was carried out in the usual manner, plotting each inspiratory volume against the corresponding change in intraesophageal pressure between the points of zero air flow at the beginning and end of the inspiration.

In each instance, measurement of the intraesophageal pressure relative to atmosphere was followed by determination of the lung compliance. Pressure volume loops of approximately normal tidal volume were then recorded and photographed at respiratory frequencies varying from 10 to 60 per minute.

Lung volumes, including the residual volume, were determined in the sitting position in all the normal subjects and in the patients with fibrosis. In addition, in the latter group, studies of ventilation, arterial blood and pulmonary oxygen uptake at rest and during a standard exercise test were carried out according to the procedure of Baldwin, Cournand and Richards [*6*]. Functional residual capacity was measured by the open circuit method [*7*].

RESULTS

Physiologic data relative to ventilation, oxygen uptake and arterial blood in the patients with fibrosis are shown in Table II, and data relative to lung volumes, maximum breathing capacity, and intrapulmonary gas mixing in Table III. The findings generally fell into that pattern previously described as characteristic of diffuse pulmonary fibrosis and alveolar capillary diffusion block [*8,9*]. Hyperventilation at rest and during exercise was a consistent observation, with resultant reduction in the oxygen uptake per liter of ventilation. The tidal volume at rest was normal or low, with relatively little increase on exercise, so that the observed hyperpnea could be accounted for on the basis of increased respiratory frequency, especially during exercise. There was a definite tendency toward elevation in oxygen uptake, but this was not present in all cases. Although normal or low normal at rest in most instances, arterial blood oxygen saturation fell during exercise, indicating a significant defect in gas exchange presumably associated with diffusion block. However, in three patients with evidence of abnormality in intrapulmonary gas mixing, it is recognized that a venous admixture effect may have been operative as well. No consistent deviations from the normal in arterial blood pH, carbon dioxide tension, or hematocrit were found in this group. The total lung capacity and the lung volume compartments were usually found to be appreciably reduced in corresponding proportion with the exception that the ratio of the residual volume to the total lung capacity tended to be slightly greater than the predicted normal. In only one patient (D. F.)

TABLE II

PHYSIOLOGIC DATA AT REST AND DURING EXERCISE RELATIVE TO VENTILATION, OXYGEN UPTAKE, AND ARTERIAL BLOOD IN NINE PATIENTS WITH PULMONARY FIBROSIS*

Case No.	Patient	Age (yr.) and Sex	Body Surface Area (sq. M.)		$\dot{V}_E/M^2$		$\dot{V}_{O_2}/M^2$		$\dot{V}_{O_2}/\dot{V}_E$		V_t		f		Sa_{O_2}		pH_s		Pa_{co_2}		V_c	
					Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
				Obs.	5.05	16.9	141	575	27.8	33.9												
I	G. R.	56, M	1.82	Pred.	3.9	11.2	132	506	38.5	53.2	460	1100	20	28	98	93	7.40	7.39	48	49	45	46
				Obs.	4.41	14.8	128	479	29	32.3												
II	A. S.	50, M	1.81	Pred.	3.9	11.2	132	506	38.5	53.2	512	672	17	40	96	89	7.42	7.42	39	38	50	50
				Obs.	6.89	16.7	207	608	30.1	36.3												
III	D. F.	49, F	1.38	Pred.	3.2	11.4	126	505	46	53.6	452	576	21	40	93	91	7.42	7.39	34	33	36	38
				Obs.	6.57	20.3	161	464	24.5	22.8												
IV	H. S.	51, M	1.85	Pred.	3.9	11.2	132	506	38.5	53.2	505	682	24	55	91	78	7.42	7.40	43	45	43	44
				Obs.	5.6	19.1	149	402	26.7	21												
V	I. E.	40, F	1.66	Pred.	3.2	11.4	126	505	46	53.6	526	587	17.7	54	83	61	7.40	7.37	36	36	54	55
				Obs.	6.28	12.05	150	348	23.8	28.8												
VI	E. S.	25, F	1.63	Pred.	3.2	8.99	126	463	45.1	60.2	358	532	28.7	37	94	73	7.40	7.34	40	43	37	40
				Obs.	5.58	11.5	146	342	26.2	29.7												
VII	L. K.	66, M	1.62	Pred.	3.9	11.2	132	506	38.5	53.2	532	620	17	30	93	85	7.40	7.39	42	42	39	40
				Obs.	5.91	15.92	143	405	24.2	25.4												
VIII	F. S.	55, F	1.50	Pred.	3.4	11.4	129	512	44.5	53.5	403	646	22	37	94	83	7.44	7.39	40	43	38	42
				Obs.	6.38	14.9	117	348	18.4	23.3												
IX	G. M.	30, F	1.66	Pred.	3.2	8.99	126	463	45.1	60.2	389	504	27.3	49	91	68	7.40	7.37	42	43	42	45

* $\dot{V}_E/M^2$ = ventilation in L. per minute BTPS per sq. M. body surface area.
$\dot{V}_{O_2}/M^2$ = oxygen uptake in ml. per minute STPD per sq. m. body surface area.
$\dot{V}_{O_2}/\dot{V}_E$ = oxygen uptake in ml. per L. of minute ventilation.
V_t = tidal volume in ml. BTPS.
f = respiratory frequency per minute.
Sa_{O_2} = arterial blood oxygen saturation in per cent.
pH_s = arterial serum pH.
Pa_{co_2} = arterial blood dioxide tension in mm. Hg.
V_c = arterial blood hematocrit.
Figures for predicted normal are mean values [5].
Obs. = Observed value.
Pred. = Predicted value.

TABLE III

PHYSIOLOGIC DATA RELATIVE TO LUNG VOLUMES, MAXIMUM BREATHING CAPACITY AND INDEX OF INTRAPULMONARY GAS MIXING IN NINE PATIENTS WITH PULMONARY FIBROSIS*

Case No.	Patient	Vital Capacity		Total Capacity		MBC/M²		RV/TC	IIPM
		ml.	% Predicted	ml.	% Predicted	L./min.	% Predicted		
I	G. R.	2540	68	4138	76	51	100	39	3.43
II	A. S.	1990	55	3685	71	59	98	46	4.08
III	D. F.	2004	77	4984	146	49	101	60	5.03
IV	H. S.	1565	41	2049	37	94	157	24	0.93
V	I. E.	1528	53	2397	63	56	107	36	1.56
VI	E. S.	1436	46	1797	46	70	115	20	0.90
VII	L. K.	996	31	2461	31	15	29	59	1.72
VIII	F. S.	1110	44	1769	48	66	146	37	0.86
IX	G. M.	1056	35	1440	38	26	46	27	0.99

* MBC/M² = maximum breathing capacity in liters per minute per square meter body surface area.
RV/TC = residual volume to total capacity ratio in per cent (normal < 40).
IIPM = index of intrapulmonary gas mixing (normal < 2.5).
All gas volumes are BTPS.

was the absolute value for residual volume greater than the predicted normal. However, the index of intrapulmonary gas mixing was slightly elevated in three of the nine patients. Elevation in gas mixing index and in the absolute value for residual volume in one patient (D. F.) were interpreted as indicating an element of associated emphysematous change in this patient. Maximum breathing capacity, although relatively well maintained, did show a reduction comparable to that in total lung capacity in two subjects (L. K. and G. M.).

In order to compare the findings in the patients with fibrosis with those in the normal subjects in terms of respiratory work it was necessary to make certain observations in the normal subjects other than those relative to pulmonary mechanics. Physiologic data relative to ventilation at rest and during exercise in the six normal subjects studied are shown in Table IV.

TABLE IV

PHYSIOLOGIC DATA RELATIVE TO VENTILATION, RESIDUAL LUNG VOLUME, AND INTRAPULMONARY GAS MIXING IN SIX NORMAL SUBJECTS

Case No.	Subject	$\dot{V}_E$		f		Vt		RV/TC	IIPM
		Rest	Exercise	Rest	Exercise	Rest	Exercise		
X	J. A.	7.46	16.5	12	19	623	867	18	1.21
XI	J. W.	7.50	20.5	9.7	11	774	1880	23	0.93
XII	C. F.	6.96	20.6	12.7	16	548	1283	26	1.09
XIII	T. R.	6.87	14.20	9	21	755	677	14	0.78
XIV	H. S.	7.0	22.2	16	31	440	716	27	0.80
XV	G. T.	6.92	14.35	10	12	692	1200	20	0.63

TABLE V

COMPLIANCE OF THE LUNG, VITAL CAPACITY, AND TOTAL CAPACITY IN SIX NORMAL SUBJECTS*

Case No.	Subject	Age (yr.) and Sex	Body Surface Area	Compliance (L./cm. H_2O)	Vital Capacity (ml.)	Total Capacity (ml.)
X	J. A.	34, M	2.10	0.384	7530	9209
XI	J. W.	32, M	1.96	0.455	5280	6864
XII	C. F.	33, M	1.95	0.345	5200	7060
XIII	T. R.	27, M	1.93	0.217	5508	6388
XIV	H. S.	24, M	1.95	0.322	5450	7425
XV	G. T.	30, M	1.80	0.312	5328	6648
	Average value	.....	....	0.339	....	....

* Values for compliance are those obtained over the range of the tidal volume. Vital and total capacities represent gas volumes BTPS.

Expressed as liters of lung volume change per centimeter of water transpulmonary pressure change, the pulmonary compliance over the range of tidal volume at rest in six normal subjects is shown in Table V. Also included in this table are the values for vital capacity and total capacity for each subject. As indicated in Table VI, compliance of the lung over the range of the tidal volume was uniformly reduced in the patients with fibrosis. None of the values fell within the normal range, varying from less than one-half the average value in the normal group to as little as 19 ml. volume change per centi-

TABLE VI
LUNG FUNCTION DATA IN CASE IV (H. S.) CLINICAL DIAGNOSIS RADIATION PNEUMONITIS AND FIBROSIS

Observation		No Therapy (2-15-54)	Cortisone Therapy (3-9-54)	Cortisone Therapy (5-10-54)
$\dot{V}_E/M^2$	Rest	6.57	.....	5.37
$\dot{V}_E/M^2$	Exercise	20.3	.....	12.6
$\dot{V}_{O_2}/M^2$	Rest	161	.....	133
$\dot{V}_{O_2}/M^2$	Exercise	464	.....	394
f	Rest	24	.....	18
f	Exercise	55	.....	....
pH	Rest	7.50	7.42	7.42
pH	Exercise	.....	7.40	7.40
Sa_{O_2}	Rest	85	91	94
Sa_{O_2}	Exercise	.....	78	84
Pa_{CO_2}	Rest	34	43	35
Pa_{CO_2}	Exercise	.....	45	38
VC	% Predicted	41	.....	67
TC	% Predicted	37	.....	65
RV/TC	.....	24	.....	29
IIPM	.....	0.93	.....	1.38
Lung compliance	.....	.031	.....	.143

meter of water transpulmonary pressure. In the normal subjects the lung compliance could be roughly correlated with the total lung capacity, whereas correlation with the vital capacity, resting tidal volume and ventilation was poor. Similarly in the patients with fibrosis the change in lung compliance was best correlated with the reduction in total lung capacity. However, correlation with the reduction in vital capacity was also good since proportionate reduction in vital and total capacities usually occurred. A clear-cut relationship between the diminution in compliance and the diffusion block to oxygen as indicated by the drop in arterial blood oxygen saturation on exercise could not be demonstrated. Nor was it possible to correlate satisfactorily the compliance change with the ventilation, tidal volume, or the degree of

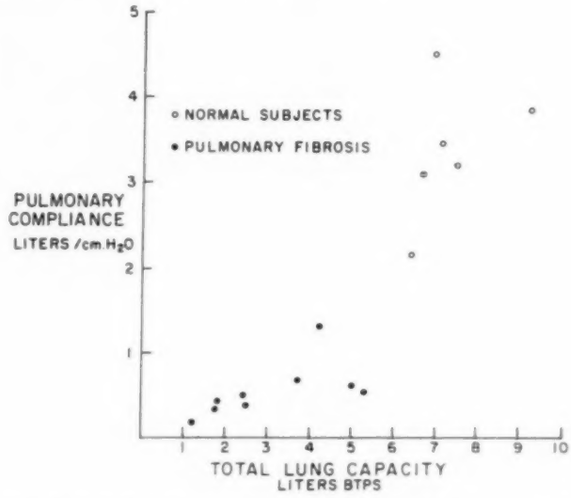


FIG. 2. Relationship between pulmonary compliance and total lung capacity as indicated by combining the data secured in normal subjects and in patients with pulmonary fibrosis.

involvement present on roentgenographic examination. The relationship between compliance and total capacity, defined by the results obtained in both the normal subjects and those with fibrosis, is shown in Figure 2.

In Table I is a comparison of the intrathoracic (intraesophageal) pressures at the end-expiratory position in the normal subjects and in those with fibrosis. The intrathoracic pressure in patients with fibrosis tended to be higher than normal, and in most instances equalled atmospheric pressure. Failure of the fibrotic lung to exert an appreciable retractile force in the end-expiratory position implies loss of normal elasticity at this volume, and is interpreted as indicating stiffening and relative fixation of the lung in this position.

Determination of pulmonary pressure volume loops in the patients with fibrosis revealed certain features which were consistent and characteristic. In Figure 3 is shown a typical pressure volume loop obtained when a patient with fibrosis executed the inspiratory capacity maneuver. To the left is shown the pressure volume loop of a normal subject for comparison. It can be seen that although the inspiratory volumes are comparable, the transpulmonary pressure at the peak of inspiration in the patient with fibrosis is over twenty times that in the normal subject. After an inspiratory volume of about 650 ml. was reached, greater negativity of intrathoracic pressure resulted in little increase in lung volume and scarcely any air movement.

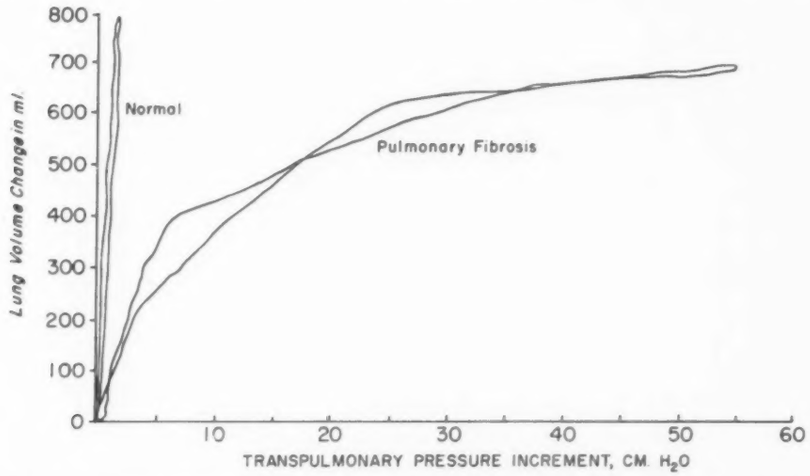


FIG. 3. Dynamic pulmonary pressure volume loops for a single breath in a normal subject and in a patient with pulmonary fibrosis. Note the sickled configuration of the patient's loop. See text for discussion.

Thus a sickled configuration of the pressure volume loop was produced, which was quite characteristic of pulmonary fibrosis as contrasted with the relatively unidirectional loop in normal subjects over the range of the inspiratory capacity.

Since the product of pressure and volume is a unit of work, it is apparent that certain areas defined by the pulmonary pressure volume loops are related to the work performed in ventilating the lung. By analysis of these areas, it is possible to further differentiate the total work into its two major components: (1) elastic work or the work necessary to overcome the elastic resistance of the lung to inflation, and (2) resistive work or the work necessary to overcome resistance to movement of air within the lung and to tissue deformation. The manner in which such analysis has been carried out is illustrated in Figure 4, showing the pressure volume loop for a single breath in a patient with pulmonary fibrosis. Since no airflow occurs at the upper tip of the loop representing the point of end-inspiration, the observed pressure at this point is that static pressure necessary to overcome the elastic resistance of the lung at this volume of inflation. A series of such points determined at varying lung volumes, defines the static pressure volume curve of the lung or the compliance, and is designated by the line within the loop extending from bottom to top near its mid-portion. At a given instant in the respiratory cycle the difference between the observed transpulmonary pressure and the compliance curve corresponds to that pressure increment required to overcome resistance to movement of air and tissue within the lung. Thus the roughly triangular area described by the compliance curve, a horizontal line from the upper tip of the loop to the ordinate, and the ordinate itself, has been taken as quantitatively related to the elastic work for any given breath. The shaded area bounded by the

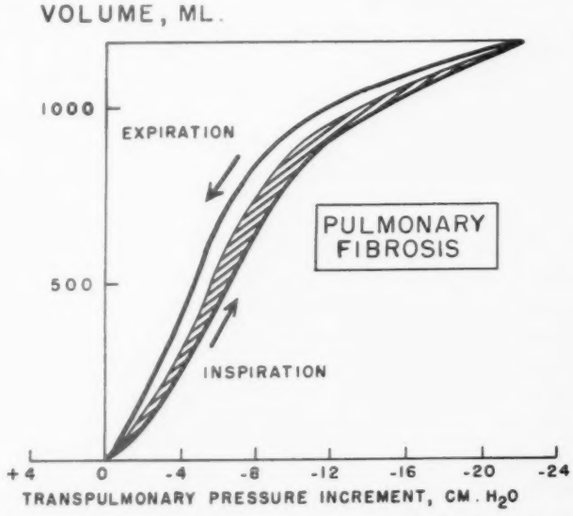


FIG. 4. Dynamic pulmonary pressure volume loop for a single breath in a patient with fibrosis. Lung volume increase in ml. from the end-expiratory position is shown on the ordinate. Transpulmonary pressure increment on the abscissa indicates the differential pressure in cm. H_2O between mouth and intraesophageal pressure, taking the latter as equivalent to intrathoracic pressure. Zero on the abscissa refers to intraesophageal pressure at the end-expiratory position, and positivity or negativity to change relative to this value. See text.

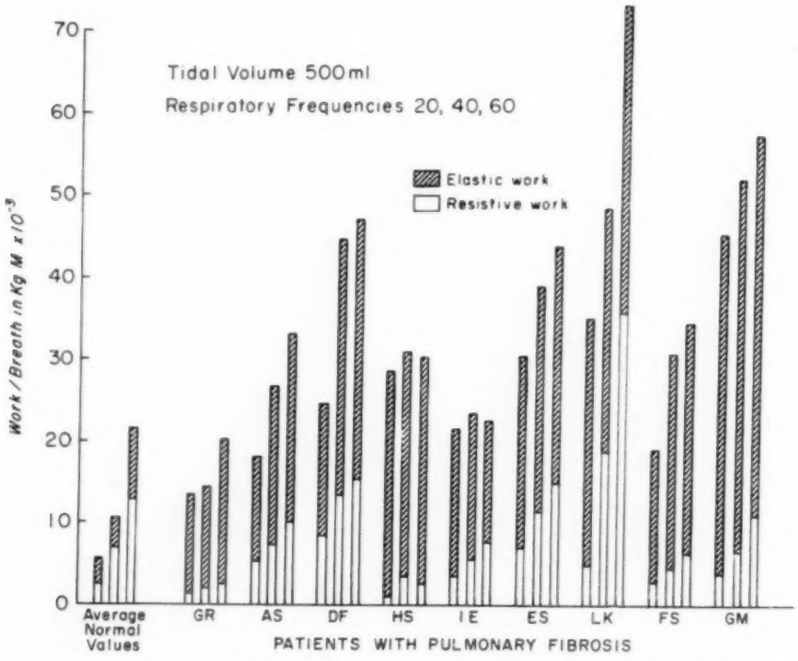


FIG. 5. Respiratory work per breath at a constant tidal volume and varying respiratory frequency in nine patients with pulmonary fibrosis as compared with the normal. Respiratory frequencies of 20, 40, and 60, respectively, are represented by the three bars for each patient. The shaded portion of the bar indicates that proportion of the total work per breath which is elastic, and the unshaded portion that proportion which is resistive.

inspiratory arm of the loop and the compliance curve has been taken as indicative of the inspiratory resistive work. The expiratory resistive work, described in the area between the expiratory arm of the loop and the compliance curve, is unshaded. In the loop shown in Figure 4, the potential energy developed in accomplishing the elastic work of inspiration is easily adequate to overcome expiratory frictional resistance, and no additional work is performed during expiration. Thus the total work per breath is related to the area bounded by the inspiratory arm of the loop, the horizontal line from the peak of the loop to the ordinate, and the ordinate itself. It should be noted, however, that respiratory work as here defined relates only to the work expenditure necessary to ventilate the lung, and is therefore only a partial determinant of the total respiratory work which must include that component required to move the chest wall and abdominal contents as well. Furthermore, since the pressure volume loops are constructed from the position of end-expiration, this type of analysis takes no account of that component of the elastic work corresponding to a rectangular area defined by the absolute value of the intrathoracic pressure (as related to atmospheric) at the end-expiratory position and the magnitude of the tidal volume. Since a part of this work is performed by the elastic recoil of the chest wall as it expands from the end-expiratory position, presumably only that portion performed by the respiratory muscles need be estimated to account for the work of breathing. However, evaluation of this latter component, requiring as it does additional knowledge of the compliance of the chest wall [*10*] was not carried out in this study.

Utilizing this method of analysis, the actual work per breath and the relative proportions of elastic and resistive work were calculated from pressure volume loops obtained at approximately the same tidal volume and widely varying respiratory frequencies in normal subjects and in patients with fibrosis. To compare the two groups, an arbitrary tidal volume of 500 ml. was chosen, and the data were plotted in each case for the observed frequencies, assuming a constant proportion between elastic and resistive components over a small tidal volume range at each frequency. In Figure 5 is shown the work expenditure necessary to ventilate the lung for a

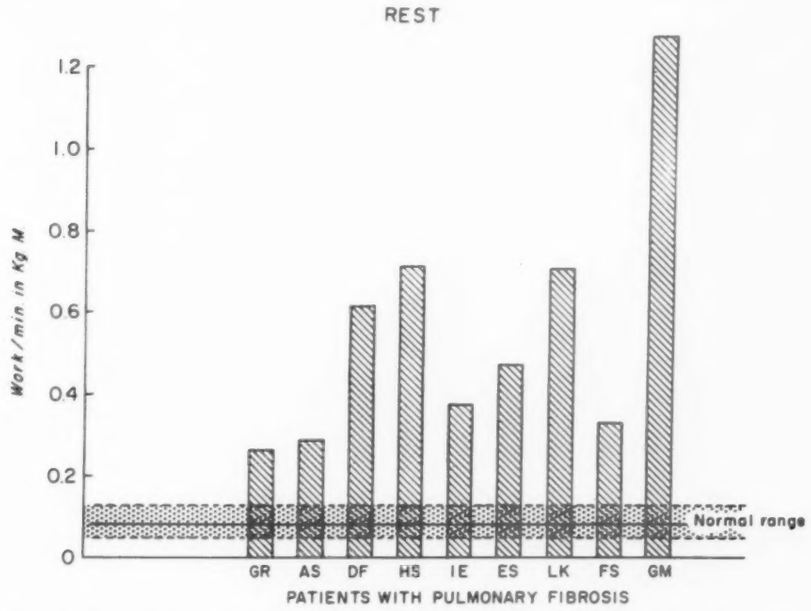


FIG. 6. Respiratory work per minute at rest in nine patients with pulmonary fibrosis as compared with the normal. In this figure and the next, the horizontal shaded bar represents the normal range, and the straight line within it the mean normal value.

single breath of 500 ml. volume at respiratory frequencies of 20, 40 and 60 per minute in both the normal subjects and those with fibrosis. Total work per breath, noted in kg. meters $\times 10^{-3}$ on the ordinate, has been subdivided into its elastic and resistive components on a simple bar graph. It can be seen that at all three frequencies the work per breath was appreciably increased over the normal in each patient with fibrosis, and that the increase came about as a result of change in the amount of elastic work.

Resistive work* in the patients with fibrosis tended to fall in the normal range with one exception (L. K.). This same patient showed marked reduction in maximum breathing capacity, suggesting that there was an additional obstructive factor in the respiratory pattern of this case.

To determine the amount of work required to ventilate the lung per unit time, calculations were based upon analysis of individual breaths of frequency and volume comparable to those actually observed at rest and during exercise. Although certain aspects of respiratory mechanics during exercise are not identical to those obtaining in this study in which voluntary changes in respiratory rate and tidal volume were utilized, conditions were considered sufficiently similar to gain from these data a roughly quantitative idea of the respiratory work required for a standard exercise test. Figure 6 shows the respiratory work per minute determined in this manner for each patient with fibrosis at rest as compared with the normal. Respiratory work was strikingly increased in the patients with fibrosis. None of the values fell in the normal range, varying from three to twelve times the mean normal value. The observed increase in respiratory work depicted in Figure 6 was based on (1) increase in the amount of work required per unit volume of pulmonary ventilation and (2) increase in pulmonary ventilation present in these patients. As shown in Figure 7, the increased respiratory work with pulmonary fibrosis was

* The elastic component of respiratory work per breath may be considered independent of respiratory rate, while the resistive component varies in direct relation to frequency. This general relationship was found in both normal subjects and in patients with fibrosis as shown in Figure 5. However, at higher respiratory frequencies the flow resistive properties of the lung exert a greater effect upon the distribution of air to its various parts, so that a progressively smaller lung volume may be effectively ventilated. The result is a decrease in the apparent or dynamic compliance at high respiratory rates, and thus an increase in the calculated work against elastic resistance. As indicated in Figure 5, at respiratory rates above 40 reduction in the dynamic compliance was found in normal subjects and in some of the patients with fibrosis.

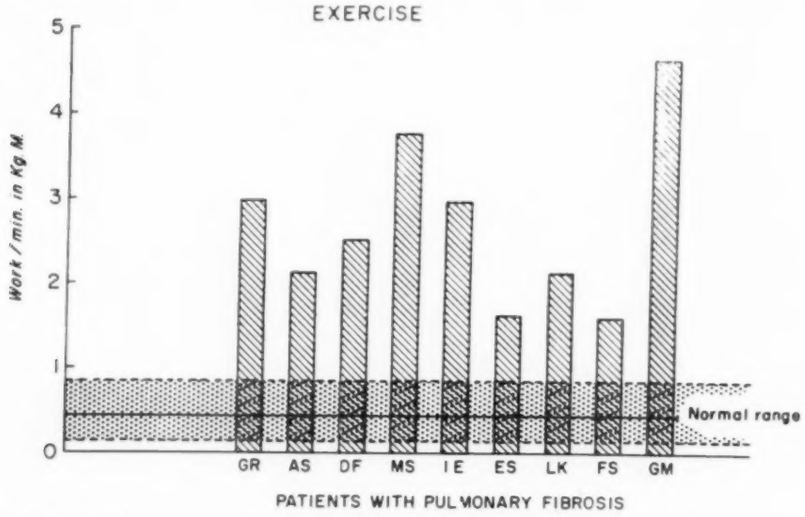


FIG. 7. Respiratory work per minute during a standard exercise test in nine patients with pulmonary fibrosis as compared with the normal.

equally impressive during exercise. Here again the observed increment was related to hyperventilation as well as to a greater expenditure per liter of ventilation.

COMMENTS

Reduction in compliance as compared with the normal at all stages of lung inflation stands out as a distinct characteristic of the fibrotic lung. Although the values for compliance in the normal group reported here are greater than those in some other series, the lung compliance values with fibrosis tend to be much less than any published for normal adults. Relatively large total lung capacities may partially account for the rather high mean value for lung compliance in this group of normal subjects. Correlation of compliance with total lung capacity rather than abnormality in gas exchange in the fibrotic lung suggests that reduced compliance is due more to changes in the interstitial tissues at wider planes than to those in the alveolar capillary membrane. So that from the mechanical viewpoint, the behavior of the fibrotic lung is that of a stiff, shrunken structure as compared with the normal.

The plateau effect occurring in the pressure volume loop of the fibrotic lung at the peak of the inspiratory capacity, with resultant sickled configuration of the loop, was a consistent observation. The degree of negative pressure developed within the thorax by these patients at the total lung capacity, as exemplified by the loop shown in Figure 3, was equal to or greater than that developed by normal subjects. This would indicate that the muscles of diaphragm and chest wall in the patients with fibrosis are capable of normal performance but that the lung reaches its limit of distensibility at a very small volume, thus markedly limiting chest expansion. It is interesting that one patient (G. M.) was capable of developing a transpulmonary pressure of 55 cm. H_2O. This is somewhat greater than that which can be developed by most normal subjects, and it is of interest that such a pressure is possible across the fibrotic lung without lung rupture. It is this limitation of lung distensibility which makes it obligatory for a patient with pulmonary fibrosis to increase his respiratory rate rather than his tidal volume to achieve the increased ventilation required at rest and during exercise.

For purposes of comparison, the elastic behavior of the fibrotic, the normal, and the emphysematous lung is described in Figure 8. The curves shown were plotted from data secured in a single representative case of each of these conditions. Total lung volume and subdivisions are represented in liters on the ordinate, and intrathoracic pressure relative to atmospheric in cm. H_2O on the abscissa. The static pressure volume relationships obtaining between the functional residual capacity and the total lung capacity are defined by the solid lines, and those between the residual volume and the functional residual capacity (over the range of the expiratory reserve volume) by the broken lines. The emphysematous lung, characterized by a large increase in residual volume at the

expense of the expiratory reserve volume, has little change in total capacity, but tends to be somewhat more compliant than the normal lung. Because of loss of lung elasticity, a lesser negativity of intrathoracic pressure than normal is developed at each stage of inflation, and the lung can be fully expanded to its total capacity by a pressure which is about half that required for the normal lung. The elastic behavior of the fibrotic lung contrasts sharply with that of the emphysematous and the normal. There is marked reduction of total lung volume and all subdivisions, although the change in vital capacity is proportionally greater than that in the residual volume. It is much less compliant than the normal lung, and inflation to its total capacity requires a pressure almost twice as great as the normal. The fibrotic lung appears to be relatively fixed at the volume corresponding to the functional residual capacity, so that it exerts a retractile force which is less than normal at this volume, and positive intrathoracic pressure may be required for further collapse to the residual volume.

Although the assumptions made in this study, and the lack of information regarding the work of moving the chest wall do not permit precise quantification of total respiratory work, the approach taken nevertheless provides a first approximation, and clearly indicates that in patients with fibrosis gross changes in the work of breathing do occur. Corroborative evidence, obtained by determination of the oxygen cost of breathing during voluntary hyperpnea, has been reported by Cournand et al. [*11*]. In a patient with diffuse pulmonary granulomatosis, these authors found that at a ventilation of 50 L. over the resting level, the increase in oxygen uptake per liter increment in ventilation was 3 ml. of oxygen per minute, or about one-third more than in the normal subject. It is probable that the elevated oxygen uptake at rest, found in some of the patients with fibrosis reported in this study and elsewhere, is related to the increased oxygen cost of breathing.

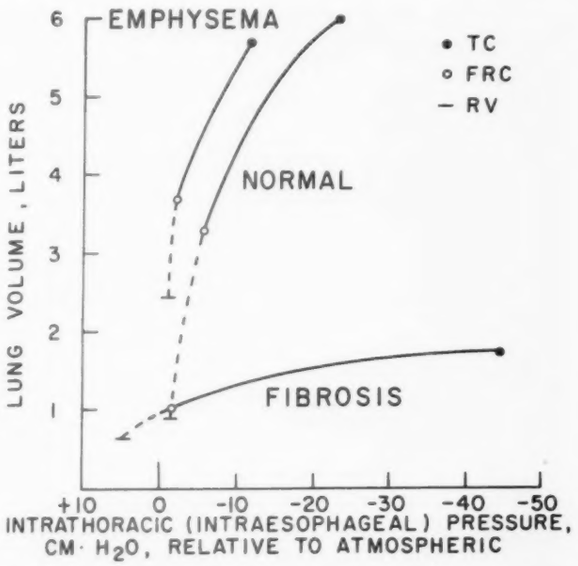


FIG. 8. Elastic behavior of the fibrotic, the normal, and the emphysematous lung. From above downward on each curve the solid circles correspond to the total lung capacity (TC), the open circles to the functional residual capacity (FRC), and the horizontal lines to the residual volume (RV). See text for discussion.

SUMMARY

In vivo measurements have indicated considerable alteration in the physical properties of the lungs involved by infiltrative or fibrotic change of various etiology. Studies in nine patients with such involvement revealed a marked reduction in pulmonary compliance as compared with the normal. Altered compliance was better correlated with reduction in total lung capacity than with abnormality in gas exchange, suggesting that changes in the interstitial tissues at wider planes are more important than those in the alveolar capillary membrane in determining the elastic behavior of the fibrotic lung. The limit of distensibility in the fibrotic lung was reached at a very small volume, and further inspiratory expansion of the chest did not occur although these patients were capable of developing a negative intrathoracic pressure equal to or greater than the normal. Resistance to airflow and tissue deformation differed little from the normal in most cases, so that the pressure volume loop described by the fibrotic lung during the inspiratory capacity maneuver assumed a sickled configuration which was quite characteristic. In the patients with pulmonary fibrosis, intrathoracic pressure at end-expiration was less negative than normal, and equivalent to atmospheric pressure in most, suggesting that the fibrotic lung had lost the normal elastic retractile force at the volume corresponding to the functional residual capacity.

The elastic behavior of the fibrotic and emphysematous lungs have been compared. In the emphysematous lung there is little change in total capacity relative to the normal, but because of loss of elasticity, the lung may be

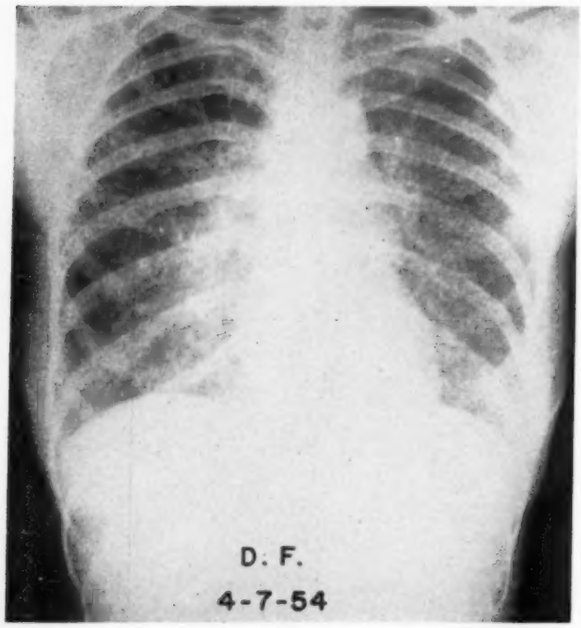


FIG. 9. Case III. Roentgenogram of the chest (D. F.). Clinical diagnosis: sarcoidosis.

expanded to its total capacity by a transpulmonary pressure as little as one-half that required for the normal lung. In the fibrotic lung there is marked reduction in lung volume, and inflation to total capacity may necessitate a transpulmonary pressure twice the normal.

Augmented elastic resistance of the fibrotic lung resulted in an abnormally high respiratory work expenditure per unit volume of inflation and therefore per liter of ventilation over a wide range of respiratory rates. The combined effects of hyperventilation and greater work per liter of ventilation made for a striking increase in the estimated work of breathing in these patients, both at rest and during exercise.

Acknowledgment: We gratefully acknowledge many helpful suggestions by Drs. Dickinson W. Richards and Jere Mead in the preparation of this manuscript.

APPENDIX

Individual summaries of clinical findings and course in nine patients with pulmonary fibrosis.

CASE I. G. R., a fifty-six year old white man had a history of exposure to asbestos for sixteen years prior to study. He had been in good health until approximately ten months prior to study when gradually increasing exertional dyspnea had appeared, together with an intractable, non-productive cough and occasional wheezing in the chest, particularly on exertion. On examination the chest expansion was somewhat reduced. Medium moist rales were heard bilaterally throughout both sides of the chest. There was an occasional sibilant rhonchus. An electrocardiogram was within normal limits. A chest film showed diffuse infiltrative change involving both lung fields. The hilar vascular markings in the lung were prominent. The heart size was at the upper limit of normal. Clinical diagnosis was asbestosis of the lung.

Little change in symptomatology or clinical findings occurred over a two year period of observation subsequent to the time of study.

CASE II. A. S., a fifty-one year old Negro man was studied in March 1954. The patient had been in excellent health until some four years prior to study when increasingly severe exertional dyspnea developed. He had no chronic cough. There was no history of exposure to toxic agents, including beryllium. On examination excursion of the chest was only slightly reduced. There were bilateral fine moist rales in the chest. Chest film showed a diffuse nodular infiltrate involving both lungs in generalized fashion, more marked in the hilar regions. The cardiac silhouette was somewhat enlarged. The clinical diagnosis was diffuse pulmonary fibrosis, etiology undetermined.

CASE III. D. F., a forty-nine year old Negro woman was studied in April 1954. She complained of polyarticular joint pain, increasing weakness and weight loss over a seven-month period prior to study. She had had a cough productive of small amounts of whitish yellow sputum for five months. She complained of only mild exertional dyspnea at the time of study. She had had a daily temperature elevation for at least several weeks. There were a few rhonchi in the left side of the chest. The liver was firm and nontender, easily palpable 4 fingerbreadths below the right costal margin in the mid-clavicular line. A firm spleen tip was palpable. An electrocardiogram was within normal limits. Kveim test was positive. A biopsy of a left supraclavicular lymph node was carried out in April 1954, with a pathological diagnosis of Boeck's sarcoid. The chest film, shown in Figure 9, revealed a nodular infiltrate throughout both lung fields with bilateral hilar lymphadenopathy. The clinical diagnosis was sarcoidosis. There was little or no change in clinical status during the period of observation for three months following study.

CASE IV. H. S., a fifty-one year old white man was first studied in February 1954. He had received radiation to the chest for a two-week period approximately three months before. He had complained of increasing dyspnea and a non-productive cough for one month prior to study. On examination there were a few crepitant rales bilaterally at the lung bases with some inspiratory retraction of the sternum and moderate limitation of chest expansion. A battery of laboratory

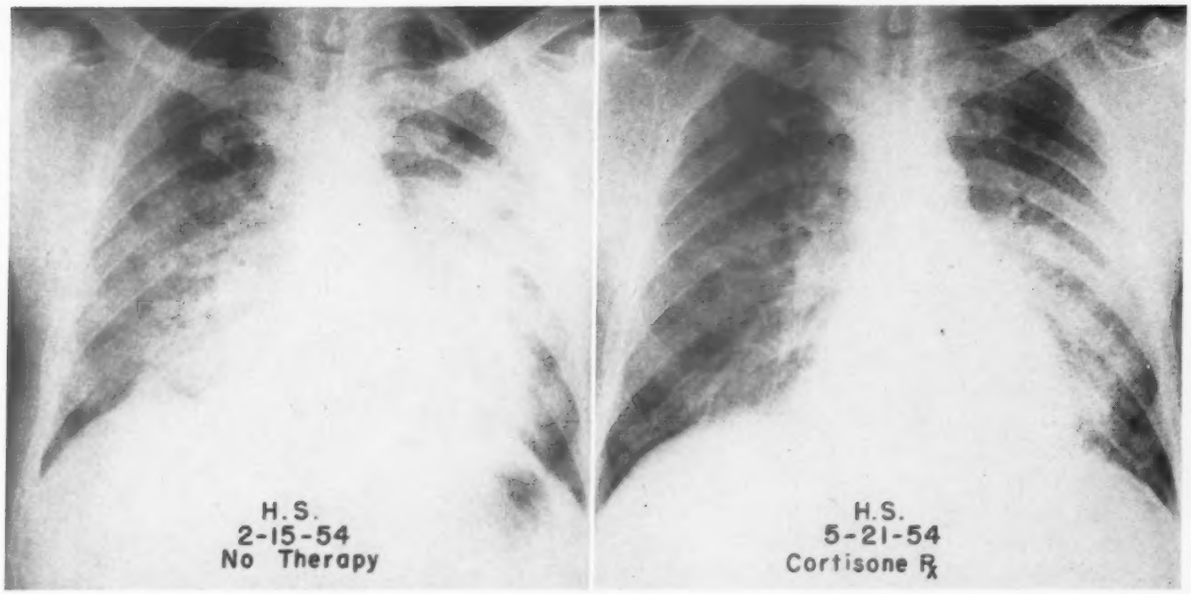


FIG. 10. Case IV. Roentgenograms of the chest (H. S.). *Left*, when first seen. *Right*, some three months later following steroid therapy. Clinical diagnosis: radiation pneumonitis and fibrosis.

tests at the time of study were all within normal limits. These included a Kveim test, sputum culture and smear for acid-fast bacilli, cytologic examination of the sputum for abnormal cells, urinalysis, serum proteins, and liver chemistry determinations, blood urea nitrogen, serum calcium and phosphorus, and an electrocardiogram. A chest film showed a nodular and confluent infiltrative process involving both lungs, principally the hilar regions and the mid-lung fields, more on the left than the right. The clinical diagnosis was radiation pneumonitis and fibrosis of the lung.

The patient was treated with cortisone and there was a rather striking subjective improvement during the ensuing three months in terms of his dyspnea and cough. As shown in Figure 10, there was considerable clearing of the densities present in both lung fields during this same three-month period. Similarly, there was a return toward normal in lung function. Table VI summarizes the data obtained during the three-month period after the patient was first seen and placed on cortisone therapy. It can be seen that the improvement in arterial oxygen saturation, vital capacity and total lung capacity during this period was accompanied by a very clear-cut change in lung compliance toward normal.

CASE V. I. E., a forty year old Latin American woman first came under observation in April 1950. At that time she gave a history of having worked in a fluorescent light factory for a four-year period from 1944 to 1948, painting fluorescent material on lamps. During the three years prior to 1950 she had had an increasing non-productive cough, and had noted exertional dyspnea and progressive weight loss with the appearance of clubbing and cyanosis of the fingers for approximately one year. Pulmonary function tests at that time showed a reduction in vital capacity to 80 per cent of the predicted normal value with some hyperventilation at rest and on standard exercise. The arterial blood oxygen saturation dropped from 94 per cent at rest to 88 per cent on exercise. There was no abnormality in acid base balance, and the index of intrapulmonary gas mixing was normal. A nodule on the right index finger which had developed following a cut by a broken fluorescent lamp bulb was removed surgically, and the microscopic diagnosis was granulomatous reaction consistent with that seen following beryllium exposure. The clinical diagnosis was berylliosis of the lung.

The patient received cortisone therapy for two years. She was not seen thereafter until June 1954, when she complained of progressively increasing exertional dyspnea for three or four months, and the edema of the ankles some three weeks prior to study. At that time a gallop rhythm was present at the cardiac apex, and the second sound at the left of the sternum at the base of the heart was markedly accentuated. There was inspiratory retraction of the sternum and scattered rales over the lower two-thirds of the chest bilaterally, with considerable limitation of chest expansion. Hepatomegaly and edema of the ankles were present. Chest films now showed the infiltrative involvement of the lungs to be more marked than in 1950, and the heart size was slightly larger. Polycythemia was present. The electrocardiogram, previously normal, now showed a shift to right axis deviation with clockwise rotation and inversion of T waves over the right precordium compatible with right ventricular hypertrophy.

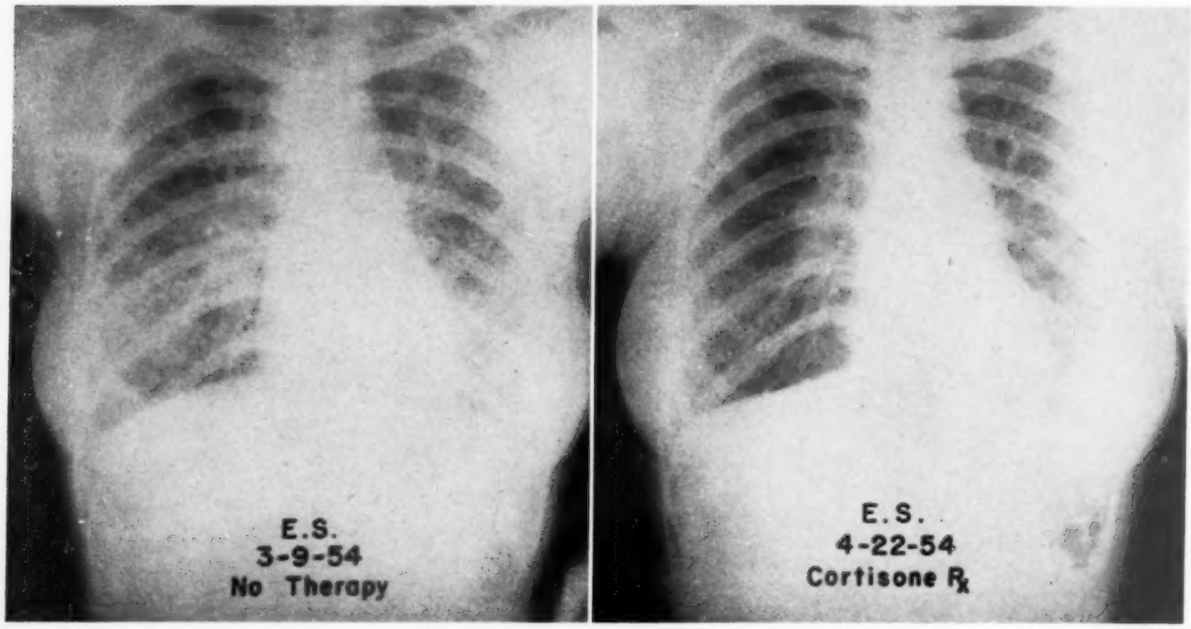


FIG. 11. CASE VI. Roentgenograms of the chest (E. S.) before and after cortisone therapy. Clinical diagnosis: sarcoidosis.

After study in June 1954, the patient was again treated with cortisone and other measures directed toward amelioration of congestive heart failure. She had shown only slight improvement two months later.

CASE VI. E. S., a twenty-five year old Negro woman first came under observation the latter part of January 1954. She had noted, for some two years previously, gradual loss of appetite and weight. For approximately one year she had experienced exertional dyspnea and some cough, usually brought on by exertion, and sometimes productive of yellowish sputum in small amounts. For three months her dyspnea had been increasingly severe so that at the time of study she was quite short of breath after climbing more than one flight of stairs. On examination there was early clubbing of the fingers. No adenopathy was noted. Chest excursion was limited bilaterally, and there were increased breath sounds present. No rales or rhonchi were heard. The second sound to the left of the sternum at the base of the heart was accentuated and split. A firm smooth liver edge was palpable 5 cm. below the right costal margin in the midclavicular line. Hyperglobulinemia was present. Roentgenogram of the chest, shown in Figure 11, revealed hilar adenopathy and extensive infiltration of both lung fields. Gastrocnemius muscle biopsy was carried out, and granulomatous lesions were demonstrated consistent with the diagnosis of sarcoid. The clinical diagnosis was sarcoidosis.

Cortisone therapy was instituted and continued for approximately six weeks. At the end of that time, as shown in Figure 11, there was some tendency to clearing of the lung fields in the chest film. Repeat pulmonary function studies were carried out some six weeks after cessation of steroid therapy. At this time the patient stated that there had been improvement in her cough, sputum production, and dyspnea. Table VII summarizes the data on lung function obtained at the time of the initial and repeat studies. Although a lesser degree of diffusion block was suggested at the time of the second study by the smaller drop in arterial oxygen saturation on exercise, there was no change in total lung capacity or in lung compliance. It would appear that pulmonary compliance in this case was better correlated with total lung capacity than with the degree of diffusion block, the appearance of the pulmonary lesions on the chest film, or the clinical findings.

CASE VII. L. K., a sixty-six year old white man first came under observation in June 1954. For twenty eight years his occupational activities had involved exposure to various types of dust. Predominantly it had been silica flour (crystalline silica) and to a much lesser extent asbestos. Symptomatically he had been well until some two years previously when he first noted dyspnea of mild degree after climbing as much as two flights of stairs. For one year prior to study he had had increasing dyspnea with a dry cough which was often precipitated by exertion. On examination there was diminished expansion of the entire chest bilaterally, more marked on the right. There was slight increase in the anteroposterior diameter of the chest. On the right there was increased tactile and vocal fremitus, dullness, generalized coarse moist rales and diminution in breath sounds. There were a few scattered rales on the left.

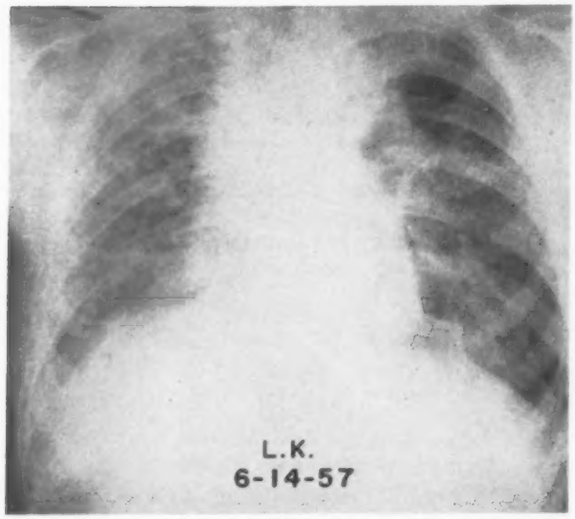


FIG. 12. Case VII. Roentgenogram of the chest (L. K.). Clinical diagnosis: pulmonary silicosis.

The patient had had regular chest examinations during the period 1935 to 1953. A review of these films indicated that between 1948 and 1953 progressive changes had developed of diffuse nodulation involving the upper right and left lung fields. The borders of the mediastinum had become more irregular in outline during this period, and sharp delineation of the left border of the heart, seen in the films of 1950, was no longer present at the time of study. The patient's chest film as it appeared at the time of study is shown in Figure 12. Extensive bacteriological studies over a period of years had failed to demonstrate the presence of tubercle bacilli. The clinical diagnosis was pulmonary silicosis.

CASE VIII. F. S., a fifty-five year old white woman was studied in June 1954. She had worked as a hospital nurse for the previous seventeen years. No unusual history of exposure to toxic agents could be obtained. She had had exertional dyspnea on climbing stairs for approximately six years, and was dyspneic on ordinary activity for one and a half years prior to study. She had had a cough productive of a varying amount of greenish yellow phlegm for two to three years. There were coarse moist rales present over the lower two-thirds of both sides of the chest anteriorly and posteriorly. A roentgenogram of the chest at the time of study showed some slight shift of the mediastinum to the left with extensive linear infiltrative change involving the lower three-quarters of both lung fields, more marked on the right. It was suspected that the patient was suffering from rather extensive bronchiectatic change with associated fibrosis of the lung, but bronchography was not carried out. The clinical diagnosis was diffuse pulmonary fibrosis, etiology undetermined.

TABLE VII
LUNG FUNCTION DATA IN CASE VI (E. S.) CLINICAL DIAGNOSIS SARCOIDOSIS

Observation		No Therapy (3-17-54)	After Cortisone Therapy (6-11-54)
$\dot{V}_E/M^2$	Rest	6.28	5.35
$\dot{V}_E/M^2$	Exercise	12.05	12.73
$\dot{V}_{O_2}/M^2$	Rest	150	147
$\dot{V}_{O_2}/M^2$	Exercise	348	402
f	Rest	28.7	24.3
f	Exercise	37	38
pH	Rest	7.40	7.42
pH	Exercise	7.34	7.39
Sa_{O_2}	Rest	94	93
Sa_{O_2}	Exercise	73	84
Pa_{CO_2}	Rest	40	38
Pa_{CO_2}	Exercise	43	39
VC	% Predicted	46	59
TC	% Predicted	46	49
$\frac{RV}{TC}$	.....	20	22
IIPM	.....	0.90	1.07
Lung compliance	.....	0.046	0.038

CASE IX. G. M., a thirty year old white woman first came under observation in April 1950. At that time she had had mild intermittent exertional dyspnea for two years progressing to severe exertional dyspnea during the six or seven months prior to admission, accompanied by paroxysmal cough, palpitation, cyanosis, nervousness, and a 40 pound weight loss. There was no history of exposure to toxic agents. She was acutely ill with moist rales throughout both sides of the chest, and a diffuse pulmonary infiltrate was evident bilaterally on the chest roentgenogram. Her arterial oxygen saturation was 65 per cent at rest and the hemoglobin was 20 gm. The clinical impression was diffuse interstitial pneumonitis, etiology undetermined. The patient was given ACTH and later cortisone with dramatic improvement.

Cortisone therapy had been discontinued some two years prior to the time of study in June 1954. At that time there was a very slight suggestion of cyanosis at rest. There was marked clubbing of the fingers and

toes, and marked limitation of chest motion and inspiratory retraction of the sternum with flaring of the lateral rib margins. A few scattered rales were present at the bases anteriorly and posteriorly. The second sound to the left of the sternum at the base of the heart was somewhat accentuated, and there was a soft systolic murmur in this area. The electrocardiogram showed incomplete right bundle branch block. A roentgenogram of the chest showed a diffuse reticular infiltrate in both lung fields with prominence of the vascular markings in the hilar regions and some elevation of the hilar vascular shadows. The clinical diagnosis was diffuse pulmonary fibrosis, etiology undetermined.

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Pulmonary Ventilation*

Blood Flow Relationships in Interstitial Disease of the Lungs

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PATHOLOGICAL thickening of the pulmonary alveolar walls interferes with diffusion of gases between alveoli and capillaries. This diffusion defect, and the limitations imposed by decreased lung compliance and restricted lung volumes, are widely recognized as the major functional disturbances accompanying interstitial pulmonary disease [*1–4*].

Rather less attention has been paid to local disturbances of ventilation and blood flow within the lungs in interstitial disease. Motley [*5*] has recently produced indirect evidence that ventilation-perfusion imbalance probably occurs in many cases, but Donald and his colleagues [*1*], after demonstrating such a ventilation-perfusion inequality, concluded that it was more apparent than real. As far as the more readily measured factor of uneven ventilation is concerned, reports are more numerous but conflicting. Baldwin et al. [*2*] were unable to demonstrate abnormalities of regional ventilation in thirty-nine cases of pulmonary fibrosis. Bates [*6*] regarded any "mixing defect" in cases of the Hamman-Rich syndrome as minimal, and he and his colleagues [*4*] found no unevenness of ventilation in most cases of diffuse pulmonary sarcoidosis. "Normal distribution of inspired gases" was regarded as one of the features of the alveolar-capillary block syndrome in a recent review [*7*]. Read [*8*], on the other hand, demonstrated uneven pulmonary ventilation in three of six cases of diffuse pulmonary fibrosis and three of five cases of diffuse pulmonary sarcoidosis.

The development of a respiratory mass spectrometer [*9*] which allows continuous analysis of up to four components of a gas mixture led to the introduction of a single-breath test of inequality of ventilation, perfusion and ventilation ratio [*10,11*]. Here we report the results of this single-breath test in a group of patients with interstitial lung disease.

SUBJECTS

Twenty-eight subjects were studied. Twenty-two were suffering from pulmonary asbestosis, which is known to produce interstitial pulmonary fibrosis [*12*] and a state of alveolar-capillary block [*13*]. Six were suffering from other conditions (one sarcoidosis, one scleroderma, one carcinomatosis, one Harmman-Rich syndrome, and two unknown disease). In all, the diffusion capacity for carbon monoxide was reduced.

The twenty-eight patients were divided into two groups, Group I, those with apparently pure interstitial disease; and Group II, those in whom the process was probably complicated by bronchial disease or emphysema. The "complicated" group consisted of those in whom the forced expiratory volume over 1 second was reduced to less than 70 per cent of the forced vital capacity ($F.E.V._{1.0}/F.V.C. < 70$ per cent [*15*]), and those whose chest roentgenogram showed obvious cysts (eleven patients). The remaining seventeen patients were regarded as suffering from "pure" interstitial disease.

TECHNICS

West and Hugh-Jones (unpublished) have modified their original single-breath test [*10,11*] and the modified technic was used in the present studies. The patient sat in a comfortable chair, breathing quietly through the mouth from a valve-box which had a dead space of about 5 ml. The tip of the mass spectrometer sampling tube lay about 2 cm. from the lips, so that a continuous record of the composition of gas passing that point was obtained.

At the end of a normal expiration, the valve-box was switched into a spirometer circuit from which the patient made a maximal inspiration of a gas mixture containing 15 per cent argon, 20.9 per cent oxygen, and the remainder nitrogen. He then made a maximal expiration at moderate speed. Throughout the procedure the mass spectrometer was adjusted to record

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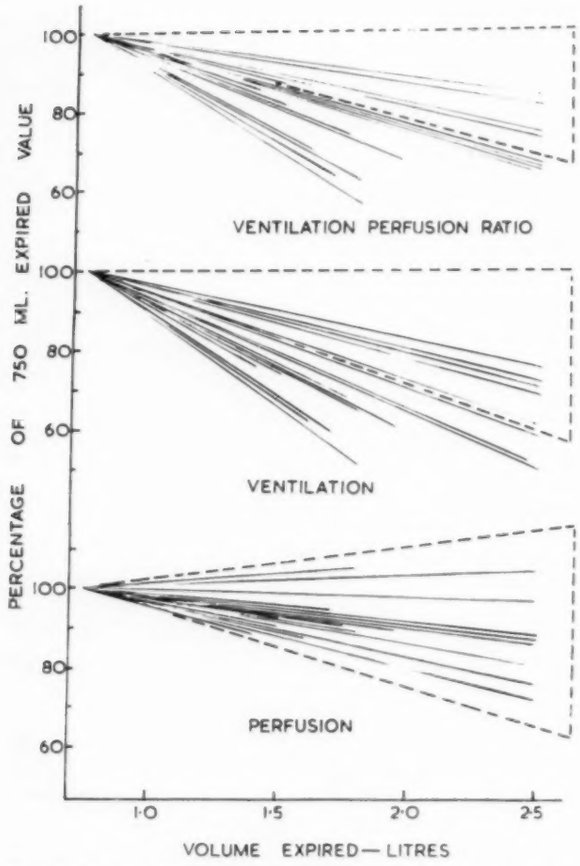


FIG. 1. Inequalities of ventilation-perfusion ratio, ventilation and perfusion in seventeen cases of pure interstitial disease. Each continuous line represents the change in that function for one patient traced through expiration (up to 2,500 ml.). The dotted lines enclose the range of normal values seen up to age fifty-five.

continuously the changing tensions of oxygen and carbon dioxide, and argon concentration. The expired volume was recorded concurrently on the fourth channel of the direct-writing recorder by integration of the signal from a wire-mesh flow-meter.

From the oxygen and carbon dioxide tensions at successive points in expiration in the resultant record, it is possible to calculate the respiratory quotient and hence the ventilation-perfusion ($\dot{V}_A/\dot{Q}_C$) ratio at those points, making use of the oxygen-carbon dioxide diagram of Rahn and Fenn [*21*]. From the argon concentration curve, the alveolar ventilation ($\dot{V}_A/V_A$ L. per unit time per L. of alveolar volume) at these same points is measured. The corresponding pulmonary blood flow values ($\dot{Q}_C/V_A$ L. per unit time per L. of alveolar volume) are calculated indirectly by dividing ventilation ($\dot{V}_A/V_A$) by ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}_C$) at each point. Alveolar volume in each case is the volume at the resting expiratory level. Full details of the basis of these calculations are given in the original report of the technic [*10,11*]. The changes in each function (ventilation, blood flow and ventilation-perfusion ratio) can then be plotted against expired volume. (Fig. 1.) The slope of the resulting line represents the unevenness of ventilation, blood flow or ventilation-perfusion ratio throughout the lungs. The steeper the slope the greater the unevenness of that particular function in different parts of the lungs.

In the original description this slope was expressed as the percentage change over 1 L. of expirate from 300 to 1,300 ml. expired. In the modified technic the point of reference is taken as the value of ventilation, perfusion or ventilation-perfusion ratio at 750 ml. expired (postdead space with maximal inspiration). The slope is then expressed as the percentage change for each 500 ml. expired from 750 ml. to the end of expiration. The greater the figure for inequality, the more uneven is ventilation, perfusion or ventilation-perfusion ratio throughout the lungs.

Each determination was performed in duplicate and the means calculated. The results were compared with normal standards from this laboratory [*16*] (approximate upper limits of normality depending upon age; ventilation inequality 6 to 14 per cent; perfusion inequality 5 to 12 per cent; ventilation-perfusion ratio inequality 6 to 9.5 per cent).

The diffusion capacity for carbon monoxide (D_{CO}) was determined by the modification of the Krogh breath-holding technic described by Ogilvie et al. [*17*]. The D_{CO} was measured in all but one patient, a man with diffuse pulmonary sarcoidosis who was short of breath, but who had a normal maximum breathing capacity. The D_{CO} in each patient was reduced below the lowest limit of normal for his body surface area. For comparison between subjects the D_{CO} in each case was expressed as a percentage of the mid-point of the normal range for that subject by the standards of Ogilvie et al. [*17*].

RESULTS

Group I. Patients with Pure Interstitial Disease (*Table* 1). Four patients (Cases 3, 5, 8 and 9; Table 1) had ventilation, blood flow, and ventilation-perfusion ratio inequalities within normal limits. The remaining thirteen showed abnormalities of one or more function. Twelve patients had uneven ventilation outside the range seen in normal subjects, and in some cases this unevenness of ventilation was very large. (For comparison, in severe emphysema, values for inequality of ventilation may reach 35 to 40 per cent per 500 ml. [*16*].) Blood flow inequality remained within normal limits in every case. Twelve subjects had abnormal inequality of ventilation-perfusion ratio. There were no differences between the patients with pulmonary

TABLE I

VENTILATION, PERFUSION AND VENTILATION-PERFUSION ($\dot{V}_A/\dot{Q}_C$) RATIO INEQUALITIES COMPARED WITH D_{CO} IN SUBJECTS WITH PURE INTERSTITIAL DISEASE

Case No.	Age (yr.)	D_{CO}*		Inequality % per 500 ml. Expired		
		Abs.	%	Ventilation	Perfusion	$\dot{V}_A/\dot{Q}_C$ Ratio†
1.	57	9.9	37	16.2 X	4.3	13.1 X
2.	56	9.8	39	22.1 X	7.3	17.1 X
3.	64	9.4	40	11.8	8.0	7.1
4.	52	10.3	41	16.3 X	−2.4	17.8 X
5.	43	13.8	47	6.7	3.8	4.0
6.	50	11.2	48	14.1 X	5.7	9.9 X
7.	59	11.9	49	14.2 X	7.1	9.8 X
8.	47	15.7	53	8.1	4.0	5.1
9.	48	13.1	58	7.9	1.1	6.9
10.	44	13.8	60	11.7 X	4.4	7.5
11.	37	13.3	63	23.4 X	5.3	20.5 X
12.	41	16.8	66	8.6	−1.3	9.1 X
13.	51	17.2	72	17.6 X	6.9	12.0 X
14.	59	8.4	37	21.6 X	3.3	19.1 X
15.	56	12.0	49	16.2 X	4.6	12.7 X
16.	71	13.0	51	18.5 X	9.1	10.7 X
17.	33	—	..	11.5 X	3.4	9.7 X
For comparison: Upper limits of normality at age:	45	....	..	10	8.7	7.5
	55	....	..	12	10.5	8.5
	65	....	..	14	12	9.5

NOTE: Cases 1 to 13, asbestosis; Cases 14 to 17, other interstitial disease.

* D_{CO}: abs. = ml. CO/minute/mm. Hg. partial pressure gradient
% = expressed as percentage of mid-point of normal range for that subject.

† X: abnormal value (compared with normal subjects of same age, see text).

TABLE II

VENTILATION, PERFUSION AND VENTILATION-PERFUSION ($\dot{V}_A/\dot{Q}_C$) RATIO INEQUALITIES COMPARED WITH D_{CO} IN SUBJECTS WITH COMPLICATED INTERSTITIAL DISEASE

Case No.	Age (yr.)	D_{CO}*		Inequality % per 500 ml. Expired		
		Abs.	%	Ventilation	Perfusion	$\dot{V}_A/\dot{Q}_C$ Ratio†
1.	59	0‡	..	35.8 X	21.9 X	18.6 X
2.	46	6.4	30	36.3 X	−5.5 X	39.9 X
3.	46	8.7	35	30.0 X	17.5 X	18.2 X
4.	55	9.3	38	19.1 X	14.8 X	7.2
5.	45	10.2	39	10.3 X	8.7	2.9
6.	45	12.4	43	15.4 X	12.0 X	7.6
7.	54	12.8	53	11.2	9.0	4.3
8.	52	14.4	56	11.9 X	0.3	11.8 X
9.	54	18.4	67	10.3	7.9	3.6
10.	56	5.8	26	42.6 X	22.1 X	23.4 X
11.	57	14.0	48	15.3 X	1.1	14.2 X
For Comparison: Upper limits of normality at age:	45	....	..	10	8.7	7.5
	55	....	..	12	10.5	8.5
	65	....	..	14	12	9.5

NOTE: Cases 1 to 9, asbestosis; Cases 10 and 11, other interstitial disease.

* D_{CO}: abs. = ml. CO/minute/mm. Hg partial pressure gradient.
% = expressed as percentage of mid-point of normal range for that subject.

† X: abnormal values (compared with normal subjects of same age, see text).

‡ D_{CO} so low as to be unmeasurable by single-breath technic.

asbestosis and those with other interstitial disease.

Excluding four patients (Cases 3, 5, 8 and 9) in whom all values were normal, and one patient (Case 12) who had an isolated inequality of ventilation-perfusion ratio, there remain twelve subjects in whom the ventilation-blood flow relationships fell into a remarkably constant pattern. This consisted of abnormal unevenness of ventilation, associated with even blood flow, with the result that the ventilation-perfusion ratio inequality was of the same order as the ventilatory inequality. This relationship is represented graphically in Figure 1. It is confirmed by the high correlation ($r = 0.904$) between ventilatory inequality and ventilation-perfusion ratio inequality.

Unevenness of ventilation did not run closely parallel with the severity of the diffusion defect (correlation coefficient between D_{CO} and ventilatory inequality $= -0.203$).

Group II. Patients with Complicated Interstitial Disease (*Table* II). There was no constant pattern of abnormality in this group. Two patients had completely normal values. Some fell into the same pattern as those in the pure interstitial group, but the most striking feature was the presence of an abnormal inequality of blood flow, in six cases which was very large in five cases. The ventilation-perfusion ratio inequality was thus the resultant of the two disordered functions of unequal ventilation and perfusion in these cases, and did not bear the same close relationship to ventilation inequality that was seen in cases of uncomplicated interstitial disease.

COMMENTS

Analysis of a single expirate reveals inequality of ventilation, perfusion, or ventilation-perfusion ratio only if regions of lung with different ventilations or ventilation-perfusion ratios empty asynchronously. If all areas empty synchronously the alveolar plateau will be flat no matter what regional inequalities are present. This concept

of "effective synchrony and asynchrony" of emptying has been amplified by West [*18*], who points out that the measured inequalities will be minimum ones. Still greater inequalities than those demonstrated may be hidden by the synchronous emptying of areas of lung with different ventilations or different ventilation-perfusion ratios. The synchrony of emptying cannot, however, artificially increase true ventilation, perfusion, or ventilation-perfusion ratio inequalities.

Similarly, it may be shown that, in interstitial disease, the presence of a diffusion defect will lead to an underestimate of the ventilation-perfusion ratio inequality. In calculating the $\dot{V}_A/\dot{Q}_C$ ratio of any area with the present technic, it is assumed that there is no end-capillary gradient for oxygen or carbon dioxide. The presence of a constant end-capillary gradient in all areas does not greatly affect the value of $\dot{V}_A/\dot{Q}_C$ inequality. But regions with a low $\dot{V}_A/\dot{Q}_C$ ratio have a greater end-capillary gradient than regions with a high $\dot{V}_A/\dot{Q}_C$ ratio; and this leads to a falsely high value for $\dot{V}_A/\dot{Q}_C$ ratio in regions of the lung in which this ratio is low. Differences between areas with low and high $\dot{V}_A/\dot{Q}_C$ ratios will thus be artificially reduced, and we derive an underestimate of the true ventilation-perfusion ratio inequality. The presence of an especially large local diffusion defect in the areas of low $\dot{V}_A/\dot{Q}_C$ ratio will still further exaggerate this factor. The calculation of alveolar ventilation from the argon tracing will not be affected, and the blood flow inequality may therefore be overestimated. The over-all effect in the present series is thus likely to be an underestimate of true ventilation and ventilation-perfusion ratio inequalities, and perhaps an overestimate of the inequality of perfusion.

These criticisms applied to the results in cases of pure interstitial disease would only serve to strengthen the pattern demonstrated in most cases: unevenness of ventilation and of ventilation-perfusion ratio in the presence of fairly uniform blood flow. In simple mechanical terms: Blood emerging from the right side of the heart is distributed evenly to all parts of the lungs. Inspired air is not evenly distributed. Some parts of the lungs receive a great deal more than others. As a result, the ratio of alveolar ventilation to alveolar perfusion varies markedly in different regions of the lungs.

Donald and his associates [*1*] concluded that the major part of the ventilation-perfusion ratio inequality which they demonstrated in cases of pulmonary fibrosis with alveolar-capillary block was more apparent than real. Unevenness of perfusion, with absence of blood flow in some ventilated areas, played a small part. To account for the larger part of the demonstrated $\dot{V}_A/\dot{Q}_C$ inequality they postulated the presence of local areas with such a severe diffusion defect that gaseous exchange in these areas was grossly reduced. Blood from such regions would then have the characteristics of blood from an area of low ventilation-perfusion ratio, and gas from such regions would appear to come from areas with a high ventilation-perfusion ratio, although both ventilation and perfusion of these regions were actually normal.

The results of the present series of experiments suggest a different interpretation. The sloping ventilation-perfusion ratio lines in Figure 1 could be produced by a genuine ventilation-perfusion ratio inequality or by the mechanism which Donald et al. postulate. However, their hypothesis requires that ventilation shall be fairly even, and from the ventilation lines of Figure 1 (which are dependent purely on argon dilution and are not subject to the diffusion factor) this is clearly not so. Quite apart from any questions of synchronous or asynchronous emptying, it is apparent from Figure 1 that regions with a high ventilation-perfusion ratio have a high ventilation and vice versa. We have seen, indeed, that throughout the pure interstitial group, unevenness of ventilation-perfusion ratio is closely correlated with unevenness of ventilation.

The demonstration of an enlarged physiologic dead space (by determining arterial P_{CO_2} and applying the Bohr equation) in such cases would indicate that a ventilation-perfusion ratio inequality exists without elucidating its mechanism. It is not permissible to interpret such an enlarged dead space as due to ventilation of unperfused alveoli and hence to postulate a perfusion imbalance, unless the physiologic dead space is very large indeed.

We would, therefore, conclude that there is a large ventilation-perfusion ratio inequality in many cases of apparently pure interstitial disease, that this inequality is dependent almost entirely on uneven ventilation, and that pulmonary blood flow seems to remain uniform. This interpretation differs from that of Donald and his colleagues. Since the technic used de-

pends on sampling expired air, the added possibility of true shunts, i.e., perfusion of completely unventilated areas, cannot be excluded.

The cause of the uneven ventilation is not immediately apparent. The degree of nonuniformity is of the same order as that seen in moderately severe emphysema [*16*]. In emphysema, the ventilatory inequality is believed to be largely due to bronchial disease, but the presence of significant airway obstruction was excluded by definition in the present cases of pure interstitial disease. It seems that local abnormalities of expansion must account for the inequality in the present series. Certainly it has been shown [*19*] that the ventilatory inequality in diffuse interstitial pulmonary fibrosis is reversible if the underlying pathologic process responds to corticosteroid therapy.

It might be objected that the present group is weighted by the presence of so many patients with pulmonary asbestosis. The objection may be a valid one. However, the results in patients with asbestosis were indistinguishable from those in subjects with well recognized interstitial disease, and Williams and Hugh-Jones [*14*] have shown that a functional state of alveolar-capillary block is an early and constant feature of pulmonary asbestosis.

In the patients with complicated interstitial disease, blood flow abnormalities were common. It is tempting to suggest that this uneven perfusion is due to superadded cysts or generalized emphysema, since one of us has demonstrated [*16*] that perfusion abnormalities are common in emphysema, especially when large cysts are present. However, since these pathologic complications are likely to arise in the more advanced and long-standing cases of interstitial disease, the possibility remains that blood flow abnormalities may occur as a later stage in the natural history of the interstitial process itself.

The demonstration of the large ventilatory and ventilation-perfusion ratio inequality in many cases of apparently pure interstitial disease is of some importance. It is possible that the failure to demonstrate ventilatory inequality in a number of series in the past [*1,2,4*] is a reflection of the insensitivity of the methods used [*20*]. Certainly it is demonstrable by a technic of moderate sensitivity, e.g., the closed-circuit helium dilution method [*8*]. The current demonstration that this ventilatory inequality (measured from the argon tracing) may lead to an appreciable ventilation-perfusion imbalance (measured independently from the oxygen and carbon dioxide tracings) confirms its significance.

The ventilation-perfusion ratio inequality may be of considerable significance in a patient already suffering from a defect of gaseous diffusion. If the regions of lung with the highest ventilation-perfusion ratio just produce normal arterial oxygen tensions in end-capillary blood, then those regions with a lower $\dot{V}_A/\dot{Q}_C$ ratio will produce low arterial oxygen tensions (and may lead to cyanosis) even in the absence of a state of alveolar-capillary block. In the presence of a generalized diffusion defect at the alveolar-capillary membrane, there is a significant gradient between alveolar and end-capillary oxygen tensions. Compared with areas of higher $\dot{V}_A/\dot{Q}_C$ ratio, the alveolar oxygen tension of regions with a low $\dot{V}_A/\dot{Q}_C$ ratio is low, and, in addition, there is a greater end-capillary gradient for oxygen in these regions. Hence, the end-capillary oxygen tensions of blood from such areas may be reduced considerably below the tensions in blood from areas with a higher $\dot{V}_A/\dot{Q}_C$ ratio. In an attempt to "adequately" ventilate the areas of low $\dot{V}_A/\dot{Q}_C$ ratio, it is necessary for the total ventilation to be markedly increased, and for the areas of higher $\dot{V}_A/\dot{Q}_C$ ratio to be wastefully over-ventilated. Hyperventilation at rest is common in cases of alveolar-capillary block. It is suggested that ventilation-perfusion ratio inequality contributes (with the diffusion defect) to arterial oxygen unsaturation commonly seen in such patients on exercise, even when hyperventilation prevents it from occurring at rest.

The non-homogeneity of "alveolar" gas which results from the ventilation-perfusion inequality obscures the significance of so-called "end-tidal" samples, and hence of end-tidal sampling methods of determining diffusion capacity [*6*]. The magnitude of the ventilatory inequality is comparable with that seen in many cases of emphysema in which the hazards of end-tidal sampling are rather better appreciated. The single-breath method of determining D_{CO} [*17*] with its allowance by helium dilution for distributional defects, theoretically offers a better approach to the problem even in these examples of apparently pure diffusion defect.

SUMMARY

Pulmonary ventilation and blood flow relationships have been studied in seventeen subjects

with apparently pure interstitial disease of the lungs, and in eleven subjects with interstitial disease complicated by cyst formation or probable emphysema.

Subjects with apparently pure interstitial disease frequently had markedly uneven ventilation of the lungs which, in the presence of uniform blood flow, led to marked ventilation-perfusion imbalance.

In subjects with complicated interstitial disease, abnormalities of pulmonary blood flow, not found in those with pure interstitial disease, were common.

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The Respiratory Effects of Progesterone in Severe Pulmonary Emphysema*

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In severe pulmonary emphysema there may be retention of carbon dioxide because of abnormalities of distribution of gas and blood to the alveoli [*1*]. When there is prolonged carbon dioxide elevation, the respiratory center in the brain loses its sensitivity to changes in the carbon dioxide tension [*2*]. In such cases, respiration is regulated to a greater or lesser degree by the effect of changes in the oxygen tension on the carotid and aortic bodies. This loss of sensitivity of the respiratory center to carbon dioxide complicates the management of such patients, as the administration of oxygen may remove the only remaining stimulus to respiration precipitating coma and apnea [*3*]. In such a situation, some method of increasing the effective ventilation and eliminating the excess carbon dioxide is needed.

Heerhaber and his associates [*4*] reported in 1948 that progesterone increased ventilation and reduced the carbon dioxide tension in normal persons. They presented evidence which suggested that progesterone increased the sensitivity of the respiratory center. Tyler [*5*] studied six patients with carbon dioxide retention due to pulmonary emphysema. He found that progesterone produced a significant increase in effective ventilation and reduced the carbon dioxide tension of the blood.

METHODS

Seven male patients with severe pulmonary emphysema, whose disease had become stable after many weeks to months of treatment, were studied. In addition, two normal men were investigated in a similar manner. The tests were performed in the postabsorptive state in the morning under basal conditions. The various subdivisions of the total lung capacity, minute ventilation, and arterial blood studies were determined with the subject in the supine position, the head of the bed elevated to a 30 degree angle. The maximum breathing capacity and spirogram of rapid inspiration and expiration were performed, with the patient standing, on a 13.5 L. Collins Respirometer. For spirograms of inspiration and expiration a kymograph speed of 32 mm. per second was used. For the maximum breathing capacity the kymograph speed was 2.66 mm. per second.

The minute ventilation and oxygen consumption were determined by the collection of expired gas in a Douglas bag. The concentration of oxygen and carbon dioxide in the expired air was obtained by analysis in a Scholander micro gas analyzer. The arterial blood was obtained from the femoral or brachial artery. The response to carbon dioxide inhalation was determined by the method of Alexander et al. [*6*] using approximately 5 per cent carbon dioxide in air, and collecting the expired gas and blood after twenty minutes of carbon dioxide inhalation. The arterial blood oxygen, the carbon dioxide content and the oxygen capacity were determined by the method of Van Slyke and Neill [*7*]. The pH was determined immediately at 37°C. using a closed glass electrode and a Beckman pH meter. The carbon dioxide tension was calculated from the Henderson-Hasselbalch equation. Alveolar ventilation was calculated by the use of the Bohr equation substituting the arterial P_{CO_2} for the alveolar P_{CO_2}.

Progesterone (50 mg. in oil) was given intramuscularly once daily. It was administered for three weeks in five of the seven patients studied, and for only one and two weeks in the other two patients because of their refusal to continue taking the progesterone and periodic tests any longer. The two subjects with normal lungs received progesterone for two and four weeks, respectively. Two sets of control studies were obtained in the week before treatment, and these were repeated at approximately weekly intervals while progesterone was given. The tests performed during progesterone therapy were carried out about twenty-four hours after the last dose of medication. The lung and ventilatory volumes are given at BTPS except for the oxygen consumption which is given at STPD.

RESULTS

In Table 1 are presented some of the characteristics of the group studied as well as the

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TABLE I

MEASUREMENTS OF AIRFLOW RATES BEFORE AND DURING PROGESTERONE THERAPY

Patient	Age (yr.)	Body Surface Area	No. of Studies		Total Vital Capacity (L.)		1 sec. Vital Capacity (L.)		Maximum Breathing Capacity (L./min.)		Maximum Expiratory Flow Rate (L./min.)		Inspiratory Flow Rate (L./min.)		Remarks
			Control	Progesterone	Control	Progesterone	Control	Progesterone	Control	Progesterone	Control	Progesterone	Control	Progesterone	
S. W.	51	1.62	2	3	1.7	1.4	.47	.47	23	20	24	18	193	126	.....
G. M.	59	1.8	2	3	1.2	1.2	.37	.33	21	23	16.2	13.4	121	120	.....
J. S.	64	1.90	2	1	1.3	...	.45	...	19	...	17.4	...	112	...	Refused further tests
G. C.	61	2.05	2	2	1.3	1.2	.31	.26	20	24	10.6	9.3	93	116	Refused further tests
M. R.	62	1.7	2	3	1.9	1.7	.47	.44	19	20	18.0	15.3	120	132	.....
R. C.	48	1.56	2	3	1.4	1.4	.34	.39	13	14	10.7	13.5	74	100	.....
A. R.	43	1.53	2	3	1.6	2.1	.25	.27	20	18	9.2	11.7	138	146	.....
P. K.	26	2.21	2	2	5.4	5.4	3.8	3.8	182	189	389	403	430	463	Normal heart and lungs
J. D.	42	1.88	2	4	4.0	3.8	2.4	2.3	130	129	281	308	340	347	Normal heart and lungs except for obliterated costophrenic angle on the right

TABLE II

MEAN VENTILATORY AND ARTERIAL BLOOD VALUES BEFORE AND DURING PROGESTERONE THERAPY

Patient	O_2 Saturation (%)		CO_2 Content (vol. %)		P_{CO_2} (mm. Hg)		pH		Total Ventilation (L./min.)		Alveolar Ventilation (L./min.)		O_2 Consumption (ml./min.)	
	Control	Progesterone	Control	Progesterone	Control	Progesterone	Control	Progesterone	Control	Progesterone	Control	Progesterone	Control	Progesterone
S. W.	93.7	92.0	49.9	45.8	40.5	39.2	7.43	7.40	9.1	10.4	3.58	4.1	200	202
G. M.	92	92.1	47.3	45.0	44.2	38.8	7.36	7.39	12.4	13.4	3.94	4.37	247	236
J. S.	95	87.3	53.9	50.2	47.4	49.2	7.39	7.36	12.1	12.9	3.33	3.57	249	265
G. C.	90.3	83.4	57.1	59.9	56.1	57.9	7.34	7.34	9.6	10.8	3.37	3.4	262	303
M. R.	89.0	89.7	62.2	54.0	53.7	50.3	7.40	7.36	11.9	13.0	3.36	3.79	273	272
R. C.	90.6	89.9	55.4	50.2	52.9	46.7	7.35	7.36	6.4	7.7	2.83	4.0	220	230
A. R.	79.2	78.9	62.4	55.7	65.4	55.2	7.31	7.33	6.9	7.7	1.88	2.76	181	212

mean values of direct and indirect measurements of air flow rates before and during progesterone therapy. In addition, the various subdivisions of the total lung capacity, including the residual volume, were determined before treatment in each subject. These are not included in the table as they are in line with the other studies. As can be seen in Table I the first seven subjects have severe pulmonary emphysema with marked reduction in the velocity of air flow on expiration and less obstruction on inspiration. The last two subjects listed were normal men and had values within the normal range. During progesterone therapy there was no change in the degree of airway obstruction as measured by these tests, which were performed to detect any bronchodilator properties of progesterone.

The effect of progesterone on ventilation and arterial blood gases in severe pulmonary emphysema is shown in Table II. The values for the two normal subjects are given in Table V. As can be seen in Table II only three of the emphysematous patients had a carbon dioxide content of less than 55 volumes per cent, or a P_{CO_2} of less than 50 mm. Hg before treatment. Carbon dioxide retention was considered moderate in two patients and severe in two others.

Table III is a summary of the data presented in Table II. The total ventilation and alveolar ventilation increased in all seven patients studied

TABLE III
EFFECT OF PROGESTERONE ON VENTILATION AND ARTERIAL BLOOD IN PATIENTS WITH PULMONARY EMPHYSEMA

Direction of Change	Min. Ventilation	Alveolar Ventilation	Oxygen Consumption	CO_2 Content	P_{CO_2}
Increased	7	7	3	0	..
Decreased	0	0	0	4	3
Unchanged	0	0	4	3	4

TABLE IV
RELATIONSHIP OF CHANGES IN P_{CO_2} FOLLOWING PROGESTERONE TO THE PER CENT INCREASE IN VENTILATION

	Increase in Total Ventilation (%)	Increase in Alveolar Ventilation (%)
P_{CO_2} fell (3 patients)	12.9	31.3
P_{CO_2} unchanged (4 patients)	10.4	8.8
Normal subjects (2)	13.7	23.3

as well as in the normal subjects. The increase in total ventilation averaged 1 L. The alveolar ventilation increased an average of 0.53 L. but one emphysematous patient (G. C.) showed only a slight rise. Oxygen consumption increased in three patients an average of 33.3 ml. (a change of 15 ml. was considered to be significant). The other four emphysematous patients and the two normal subjects showed no change in oxygen consumption during progesterone administration. The carbon dioxide content fell significantly (over 4 volume per cent) in four patients whereas only three showed a significant fall in carbon dioxide tension (over 5 mm. Hg). Although both the normal individuals had a significant decrease in P_{CO_2}, only one had a fall in carbon dioxide content of over 4 volume per cent. The pH changed an insignificant degree, one patient having an increase of 0.03 units, two a fall of 0.03 units, and another a fall of 0.04 pH units. The normal subjects had a rise of 0.02 and 0.03 pH units, respectively, during progesterone therapy. The arterial oxygen saturation was unchanged by progesterone. In spite of the change in ventilation and carbon dioxide produced by progesterone none of the patients would admit to any symptomatic improvement.

In three patients the maximum ventilatory effects occurred after one week of progesterone therapy; in two patients after two weeks, and the remaining two patients showed little change from week to week although the maximum values occurred in the third week. One of the normal subjects had the maximum ventilatory effect after one week of progesterone therapy, and the other after two weeks of progesterone therapy. All the subjects tested showed a significant increase in ventilation by the second week of progesterone administration. Two patients and one normal subject did not have a significant rise in the first week of progesterone therapy.

In an effort to account for the failure of P_{CO_2} reduction in some of the emphysematous patients in spite of hyperventilation, the per cent increase in total ventilation and alveolar ventilation was determined, and the results are shown in Table IV. The patients were divided into two groups according to the pattern of their ventilatory response to progesterone and its effect on carbon dioxide tension. The three patients with a significant fall in P_{CO_2} had a slightly greater percentage increase in total ventilation than those with no significant fall in P_{CO_2}. More significantly the percentage increase in alveolar ventilation was much greater than that in total ventilation. Two of these three patients had a markedly greater increase in alveolar ventilation than total ventilation, while in one (G. M.) the difference was only moderate. The two normal subjects showed a similar pattern. The patients with no significant fall in P_{CO_2} had an approximately equal rate of increase of both total and alveolar ventilation. The increased oxygen consumption in three of the patients does not account for the failure of the P_{CO_2} to fall, as one of the three (A. R.) had a 10 mm. Hg fall in P_{CO_2}. Of the four patients in whom the P_{CO_2} failed to fall, only two had a significant increase in oxygen consumption. The tidal volume increased in four patients, two of whom had a fall in P_{CO_2}.

Studies were made to determine if progesterone produced a change in the sensitivity of the respiratory center to carbon dioxide tension. This was done by determining the response to the inhalation of approximately 5 per cent car-

TABLE V

RESPONSE TO INHALATION OF CARBON DIOXIDE

Period	CO_2 Content (Vol. %)		P_{CO_2} (mm. Hg)		pH		Total Ventilation (L./min.)		Alveolar Ventilation (L./min.)		$\frac{\Delta \text{ Alveolar Ventilation}}{\Delta P_{CO_2}}$	O_2 Consumption (ml./min.)		Remarks
	Air	CO_2	Air	CO_2	Air	CO_2	Air	CO_2	Air	CO_2		Air	CO_2	
Patient P. K.														
Control	46.0	50.0	41.6	52.6	7.38	7.31	10.1	39.4	6.3	24.5	1.65	327	314	Normal male; 6% CO_2 mixture
	47.0	51.0	38.3	49.8	7.43	7.34	7.5	37.3	4.57	23.87	1.68	270	270	inhaled 20 minutes
Progesterone	42.4	49.3	31.8	49.5	7.46	7.32	11.9	44.7	9.1	37.0	1.58	320	301	.....
	42.3	47.9	35.6	48.9	7.42	7.38	8.5	42.6	5.5	36.7	2.34	291	296	
Patient J. D.														
Control	44.8	49.9	35.3	50.2	7.45	7.33	9.7	38.3	5.61	29.15	1.58	275	277	Normal male; 6% CO_2 mixture
	44.5	49.2	36.0	49.8	7.43	7.32	9.9	34.1	5.45	25.88	1.48	269	254	inhaled 20 minutes
Progesterone	39.5	45.0	33.0	49.0	7.41	7.30	9.9	46.6	5.77	34.0	1.76	262	283	.....
	44.1	49.0	30.4	45.5	7.50	7.36	12.0	43.2	7.2	35.93	1.90	...	...	
	40.1	47.5	29.1	48.3	7.48	7.32	11.2	48.5	6.48	19.15	.....	269	299	5.7% CO_2 mixture inhaled 20
	42.2	46.4	30.4	47.2	7.48	7.31	9.9	39.8	5.49	12.85	.....	259	334	minutes
Patient S. W.														
Control	50.8	54.7	39.0	50.8	7.45	7.36	9.3	18.5	3.74	7.70	.335	201	411	Severe emphysema; 4.5% CO_2
	49.1	51.3	42.1	53.1	7.40	7.31	8.9	17.8	3.42	5.75	.23	198	386	mixture inhaled 20 minutes
Progesterone	47.7	51.8	41.2	54.8	7.40	7.30	10.9	18.4	4.54	6.71	.16	203	364	
	46.4	51.3	40.1	54.8	7.40	7.30	9.6	19.4	3.82	7.71	.265	207	473	4.5% CO_2 inhaled 15 minutes
	43.4	49.8	36.4	53.4	7.41	7.29	10.5	22.4	3.94	8.2	.25	194	447	4.5% CO_2 inhaled 12 minutes

bon dioxide in air. The two normal subjects (P. K. and J. D.) and a patient with severe pulmonary emphysema (S. W.) were tested. The data obtained during the control and progesterone therapy periods is presented in Table v. The average ventilatory response curve per mm. Hg change in P_{CO_2} for one of the normal subjects (P. K.) is shown in Figure 1. The response curve for (S. W.), who has severe emphysema, is shown in Figure 2.

In one normal subject the carbon dioxide response curves for both alveolar and total ventilation were pushed to the left during progesterone therapy and the curves remain approximately parallel. The slightly greater increase in ventilation per mm. Hg rise in P_{CO_2} during administration of progesterone is not enough to be considered significant. This holds true for both alveolar and total ventilation. The findings in the other normal subject (J. D.) were the same as those illustrated in Figure 1, except that in the last two studies the calculated alveolar ventilations during carbon dioxide inhalation were much smaller than expected. The total ventilation was at the anticipated value and the first four determinations of alveolar ventilation produced curves similar to those shown in Figure 1. The two low values could have been due to a small error in pH as in each instance an increase of 0.04 pH units would increase the alveolar ventilation to the expected level. It has been pointed out by Riley et al. [8] that when the tidal volume approaches 2 L., a small error in P_{CO_2} determination leads to a large error in the dead space calculation.

The patient with emphysema (S. W.) had less of a response to carbon dioxide inhalation in spite of the fact that his P_{CO_2} was normal. Again the curves before and during progesterone treatment are roughly parallel and shifted to the left. The slope of the curve for total ventilation is steeper than that for alveolar ventilation. In addition, it can be seen in Table v that whereas oxygen consumption, did not increase appreciably in the normal subjects, it doubled in the patient with emphysema during carbon dioxide inhalation. The poor response to changes in P_{CO_2} in this patient should not necessarily be

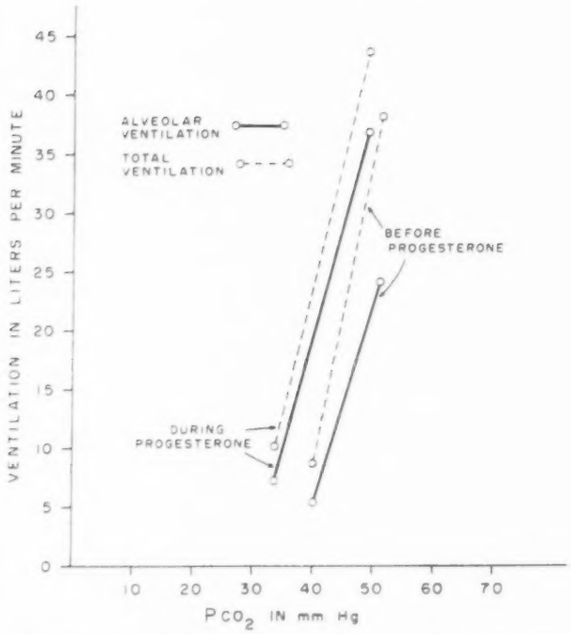


FIG. 1. Patient P. K. Response to carbon dioxide inhalation before and during progesterone therapy.

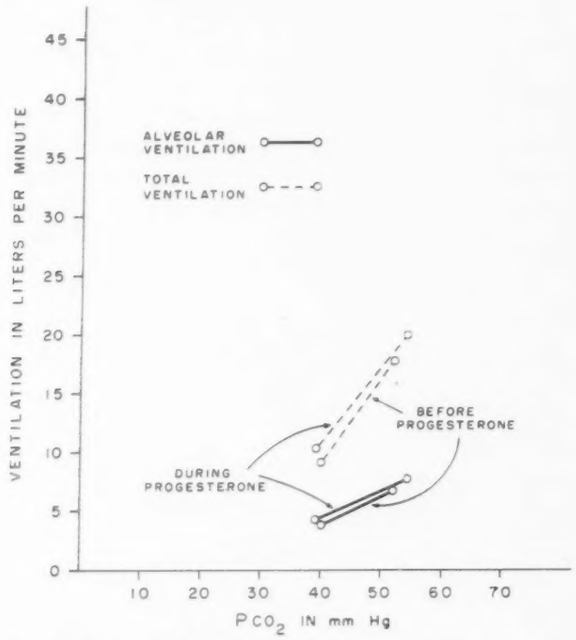


FIG. 2. Patient S. W. Response to carbon dioxide inhalation before and during progesterone therapy.

attributed to reduced sensitivity of his respiratory center as he approached his maximum breathing capacity (23 L./minute) during carbon dioxide inhalation and, therefore, was probably unable to respond to stimuli from the respiratory center. In fact, the last two times the patient was tested, expired gas and arterial blood collection had to be started after only fifteen and twelve minutes, respectively, of carbon dioxide inhalation because he could not continue the test procedure. Perhaps, if a lower concentration of carbon dioxide had been inhaled, a steeper curve could be produced.

COMMENTS

In confirmation of Tyler's report [*5*], progesterone was found to produce hyperventilation in patients with severe pulmonary emphysema and in the normal subjects studied. However, the hyperventilatory effect found in the present study of a 1 L. increase in total ventilation and 0.53 L. increase in alveolar ventilation, was less than that reported by Tyler who found an increase of 1.67 and 0.9 L., respectively. In contradistinction to Tyler, who found that the carbon dioxide tension fell in all the patients he studied, only three of the seven patients with emphysema in the present study had a significant fall in carbon dioxide tension.

The failure to develop a significant fall in P_{co_2} in some of the patients in the present study is probably due to the pattern of their hyperventilatory response to progesterone. The normal subjects and those with emphysema who had a significant fall in P_{co_2} had a greater increase in alveolar ventilation than in total ventilation, whereas the four patients with emphysema who had no fall in P_{co_2} had an equal increase in alveolar ventilation and total ventilation. In addition to the differences in the pattern of the ventilatory response in those with a significant fall in P_{co_2}, as contrasted with those in whom the P_{co_2} was unchanged, there are probably other factors involved such as the potentiality for change in ventilation-perfusion relationships. Increased work of breathing as a result of hyperventilation during progesterone therapy did not seem to be a significant factor in the failure of the P_{co_2} to fall.

The site of action of the hyperventilatory effect of progesterone still needs to be precisely demonstrated. Landau and his co-workers [*9*] have studied the metabolic effects of progesterone. The principal effect seemed to be nitrogen loss. There was no evidence that this catabolic effect was due to stimulation of the adrenal or thyroid gland. They found no increase in urinary 17-ketosteroids during progesterone administration. Studies made to detect any bronchodilator

effect of progesterone, that might be mediated through the adrenal gland, were unchanged by the administration of progesterone. However, since the patients had pulmonary emphysema and not reversible asthma, a great change in the rate of expiratory air flow could not be expected. Oxygen consumption increased in three of the seven emphysematous patients in the present study. Tyler [*5*] also found that the oxygen consumption increased in three of his six patients during progesterone administration. This increase in oxygen consumption does not indicate that the hyperventilatory effect of progesterone is due to stimulation of the thyroid. Oxygen consumption was not increased in the normal subjects studied by Heerhaber et al. [*4*], Landau [*9*], or in those in the present study. Changes in oxygen consumption were unrelated to the degree of hyperventilation produced by progesterone. It appears likely that the increased oxygen consumption occurring in some emphysematous patients during progesterone therapy is due to the increased work of breathing produced by the hyperventilation. It is well known that in severe pulmonary emphysema, there is an increase in the work of breathing [*10,11*].

An attempt was made in this study and in that of Heerhaber et al. [*4*] to determine if the hyperventilatory effect of progesterone was produced by increasing the sensitivity of the respiratory center to changes in carbon dioxide tension. Heerhaber and co-workers measured the response in normal subjects of the inhalation of 2 to 5 per cent carbon dioxide twenty-four hours after an injection of progesterone. They compared the changes in total ventilation to those in P_{CO_2}. In the present study the carbon dioxide response curve to approximately 5 per cent carbon dioxide in air was determined after a week or more of progesterone therapy in two normal subjects and in one with severe pulmonary emphysema. In confirmation of the work of Heerhaber et al. [*4*], it was established that in normal persons the carbon dioxide response curve is shifted to the left. This was found to be true for both the total ventilation and alveolar ventilation. The increase in alveolar ventilation per mm. Hg rise in P_{CO_2} was slightly greater during progesterone administration than during the control studies. However, in both this study and that reported by Heerhaber et al. [*4*], the change in the increment of ventilation per mm. Hg rise in P_{CO_2} is too small to be considered conclusive. A more sensitive method of measuring the sensitivity of the respiratory center may be needed to detect with certainty small changes in its ability to respond to normal stimuli. It has been clearly demonstrated that during progesterone administration, the respiratory center is set at a lower threshold of response to carbon dioxide tension, such as one finds at a high altitude. It has not been conclusively shown whether this shift of the carbon dioxide response curve to the left is a direct effect of progesterone on the sensitivity of the respiratory center, or an adjustment of the respiratory center to hyperventilation stimulated elsewhere by progesterone. The one emphysematous patient (S. W. whose P_{CO_2} was normal) studied in this manner showed changes qualitatively similar to those in normal man, but quantitatively different.

It appears that progesterone (at least in the dose of 50 mg. in oil daily) can reduce the carbon dioxide tension in some, but not all, emphysematous patients. This may prove to be of therapeutic value in instances of carbon dioxide retention, in spite of the lack of demonstrable symptomatic improvement in the patients studied. However, its hyperventilatory effect does not occur quickly. In the present study, the hyperventilatory effect was sometimes not demonstrated until the second week of progesterone administration, although Heerhaber et al. [*4*] noticed an effect in twenty-four hours. It is not certain from this, or the other studies, if the hyperventilatory effects of progesterone would continue during long term therapy. They did continue for three weeks. The one normal subject (J. D.) studied after four weeks of progesterone therapy had a return of his ventilation to pretreatment levels by the fourth week although his P_{CO_2} was still reduced. It may be that an intermittent type of therapy will be advisable. The other problem is the catabolic effect of progesterone in already debilitated patients. According to Landau et al. [*9*], the catabolism persists throughout therapy and with long term use large amounts of nitrogen are lost. This is another reason why interrupted therapy might be indicated.

SUMMARY

1. Daily administration of intramuscular progesterone in oil produced an increase in both the total ventilation and alveolar ventilation in seven patients with severe pulmonary emphysema and in two normal subjects.

2. This hyperventilatory effect of progesterone was accompanied by a significant fall in carbon dioxide tension in only three of the seven emphysematous patients studied.

3. It seems that the alveolar ventilation must show a greater percentage increase than the total ventilation in order for the carbon dioxide tension to be reduced.

4. In three of the seven emphysematous patients studied, the increased ventilation was associated with an increased oxygen consumption. It is believed this increased oxygen consumption was due to increased work of breathing as a result of hyperventilation.

5. There was no evidence of a bronchodilator effect of progesterone.

6. Although the ventilatory response to carbon dioxide inhalation demonstrated a lower threshold to carbon dioxide during progesterone therapy, the evidence was inconclusive as to whether progesterone actually increased the sensitivity of the respiratory center.

7. The one emphysematous patient studied showed less of a response to carbon dioxide inhalation than the normal subjects. This diminished response was not felt to indicate necessarily a decreased sensitivity of the respiratory center, as it may have been due to both the fact that his oxygen consumption doubled and that his total ventilation approached his maximum breathing capacity.

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The Oxyhemoglobin Dissociation Curve in the Common Hemoglobinopathies*

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A PREVIOUS study from this laboratory indicated that there was a shift to the right of the oxyhemoglobin dissociation curve in sickle cell anemia [*1*]. This was considered to be the primary factor responsible for the arterial oxygen unsaturation frequently observed in this disease. Our initial observations on three patients with pure S hemoglobin have been extended by the study of several other patients with partially or totally abnormal hemoglobin.

MATERIAL AND METHODS

Twelve patients were studied. (Table I.) The hemoglobin pattern was established by electrophoretic analysis and alkali denaturation. Three patients had patterns characteristic of sickle cell anemia. They had either S-S hemoglobin or S hemoglobin with small quantities of fetal hemoglobin. All three were moderately anemic, but the severity of the disease varied greatly. One patient (J. J.) was completely disabled by frequent crises requiring hospitalization and transfusion. Another (D. B.) had occasional crises between which he was symptom free. The third patient (E. Y.) had never suffered a recognized episode of crisis and was able to lead an unrestricted life in spite of a hemoglobin level less than 10 gm. per 100 ml. Two patients had hemoglobin C-S disease with approximately equal amounts of C and S hemoglobin. Both had mild anemia with numerous target cells. Three patients had a slight predominance of A hemoglobin (about 55 per cent); the remainder was S hemoglobin. Three patients had the same slight predominance of A hemoglobin with the balance C hemoglobin. Of the six patients with A-S or A-C hemoglobin only one (W. L.) had a slight anemia which was probably unrelated to the abnormal hemoglobin. Another patient (C. M.) had 70 per cent S, 25 per cent A hemoglobin, 5 per cent F hemoglobin, and moderate anemia. He was classified, according to current hematologic concepts, as having both the sickle cell and thalassemia trait.

TABLE I
HEMOGLOBIN CONTENT AND ELECTROPHORETIC PATTERN

Patient	Hemoglobin (gm./100 ml.)	Electrophoretic Pattern (%)		
		A	C	S
C. S.	15.1	58	..	42
H. A.	15.2	54	..	46
L. S.	14.5	61	..	39
J. A.	14.1	57	43	...
A. R.	15.6	55	45	...
W. L.	11.1	55	45	...
S. S.	10.9	..	57	43
H. M.	10.4	..	48	52
J. J.	6.5	..	..	100
D. B.	8.4	..	..	100
E. Y.	9.7	..	..	100
C. M.*	10.3	25	..	70

* Sickle cell trait thalassemia.

Pulmonary function tests of ventilation, distribution and diffusion were performed in each patient (Tables II and III), and several points on the *in vivo* oxyhemoglobin dissociation curve were established by determining the oxygen tension, oxygen saturation, and pH of blood obtained while the patient breathed different concentrations of oxygen. One patient with S-S hemoglobin (J. J.) was restudied following transfusion. Most of the determinations were performed on arterial blood. In order to obtain points toward the lower end of the dissociation curve an occasional determination was performed on venous blood. Before arterial blood samples were collected a steady state was achieved by permitting the patient to breathe each gas mixture for twenty-five to thirty minutes. The oxygen tension studies were performed by the bubble equilibration technic of Riley, Proemmel and Franke [*2*]. Blood gas content was measured by the Van Slyke manometric method, and pH was determined with a Cambridge Research Model pH meter. The details of the technics

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TABLE II

PULMONARY FUNCTION STUDIES

Patient	Hemoglobin Pattern	Vital Capacity (% predicted normal)	Three-Second Vital Capacity (%)	Maximum Breathing Capacity (% predicted normal)	Residual Volume (% predicted normal)	Residual Volume / Total Lung Capacity	Resting Arterial O_2 Saturation (%)
C. S.	A-S	86	91	70	...	...	92.7
H. A.	A-S	81	99	103	...	...	95.1
L. S.	A-S	100	92	42	145	.32	92.1
J. A.	A-C	80	99	109	...	...	93.9
A. R.	A-C	122	100	123	...	...	95.1
W. L.	A-C	84	86	40	68	.19	93.3
S. S.	C-S	109	96	81	...	...	91.4
H. M.	C-S	81	97	98	44	.13	87.1
J. J.	S-S	72	93	75	98	.26	72.4
D. B.	S-S	82	100	106	115	.28	87.5
E. Y.	S-S	72	100	74	67	.21	89.1
C. M.	S-A thalassemia	48	72	24	190	.70	87.7

TABLE III

ALVEOLAR-ARTERIAL GRADIENT STUDIES AT TWO LEVELS OF INSPIRED OXYGEN

Patient	Hemoglobin Pattern	% Inspired O_2	Alveolar PO_2 (mm. Hg)	Arterial PO_2 (mm. Hg)	A-A Gradient (mm. Hg)	Arterial O_2 Saturation (%)
C. S.	A-S	20.88	98	66	32	92.7
		11.84	48	49	−1	77.6
H. A.	A-S	20.88	100	106	−6	95.1
		13.86	59	62	−3	88.0
L. S.	A-S	20.89	105	87	18	92.1
		16.41	71	71	0	90.2
J. A.	A-C	20.88	98	80	18	93.9
		11.84	43	36	7	70.5
A. R.	A-C	20.88	104	96	8	95.1
		11.84	45	40	5	78.3
W. L.	A-C	20.88	99	100	−1	93.3
		11.84	40	39	1	77.1
S. S.	C-S	20.88	100	99	1	92.2
		13.86	52	52	0	68.3
H. M.	C-S	20.88	105	76	29	87.1
		11.84	49	36	13	48.0
J. J.	S-S	20.89	98	85	13	72.4
		17.93	79	68	11	69.2
D. B.	S-S	20.94	105	91	14	87.5
		17.93	85	77	8	75.5
E. Y.	S-S	20.89	97	82	15	89.1
		13.91	54	51	3	64.5
C. M.	S-A thalassemia	33.95	188	105	83	96.2
		20.88	105	67	38	87.7

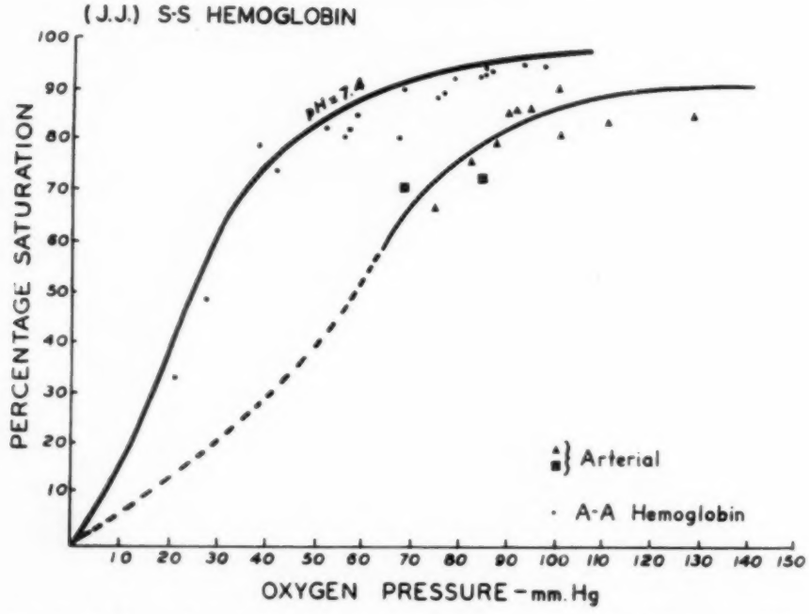


FIG. 1. Twelve points on the dissociation curve of patient J. J. with severe sickle cell anemia, together with the normal *in vitro* curve of Dill at pH 7.40 (solid black line) and nineteen points determined in our laboratory (using an *in vivo* bubble equilibration technic for oxygen tension) in five subjects with A-A hemoglobin.

used in our laboratory have previously been reported [*1*].

RESULTS

All five patients with entirely abnormal hemoglobin (three patients with S-S, two patients with C-S hemoglobin) had a resting arterial oxygen saturation below 92 per cent (Table II), the lower limit of normal in our laboratory. Since the resting arterial oxygen tension was high enough in all five patients to result in a normal oxygen saturation, the observed unsaturation could not be attributed to disease of the heart or lungs but must have been the result of an altered affinity of the hemoglobin for oxygen. This altered affinity was manifested by displacement of the oxyhemoglobin dissociation curve downward and to the right so that at any given arterial oxygen tension the hemoglobin bound less oxygen than it would if it followed the pattern of the standard dissociation curve. In Figure 1 are plotted twelve points determined on arterial blood on the dissociation curve of the patient with the severest sickle cell anemia (J. J.). The curve drawn through these points resembles the normal dissociation curve in configuration, but is displaced far to the right. Plotted for comparison are the familiar oxyhemoglobin dissociation curve of Dill at pH 7.40 and nineteen points determined in our laboratory in five subjects with normal A-A hemoglobin. Our normal curve obtained with an *in vivo* technic for oxygen tensions coincides closely with the curve of Dill which was established using an *in vitro* tonometric technic [*3*].

An oxygen tension of 70, which corresponds to a saturation of 92 per cent on the normal curve, results in a saturation of about 70 per cent in patient J. J. because of the displacement of the curve. To reach 92 per cent saturation he would have to attain an arterial oxygen tension over 150 mm. Hg, a level which cannot be reached by even the most violent hyperventilation while breathing ambient air. On inhalation of 100 per cent oxygen, however, the arterial blood of this patient and of the other four patients with entirely abnormal hemoglobin, became fully saturated indicating that the curve continues to slope upward.

Sixteen arterial and three venous points determined on a second patient with sickle cell anemia (D. B.) are plotted in Figure 2 with the nineteen normal points for comparison. The curve projected from the patient's nineteen points is markedly displaced.

Nine arterial points determined on the patient with the mildest sickle cell anemia are plotted in Figure 3 with the normal points for comparison.

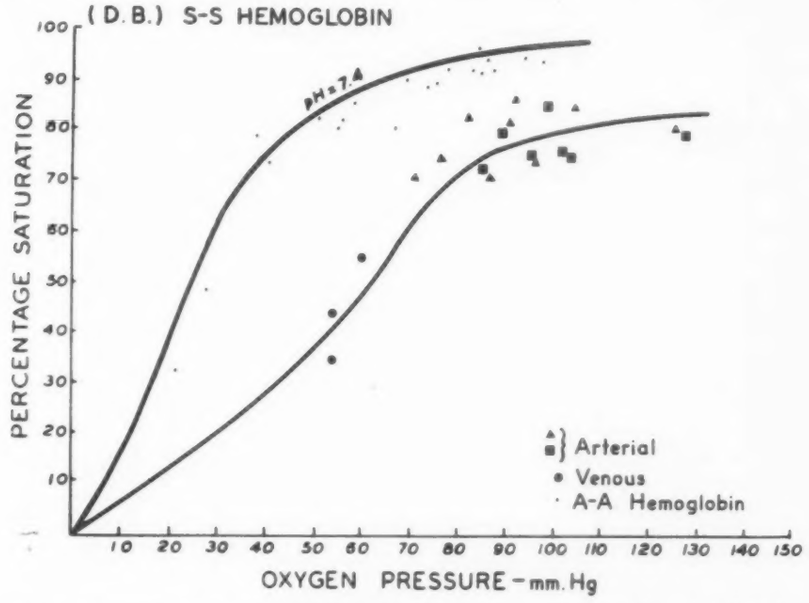


FIG. 2. Sixteen points for arterial blood and three for venous blood on the dissociation curve of patient D. B. with moderately severe sickle cell anemia, together with the normal curve of Dill and the nineteen points determined in five subjects with A-A hemoglobin.

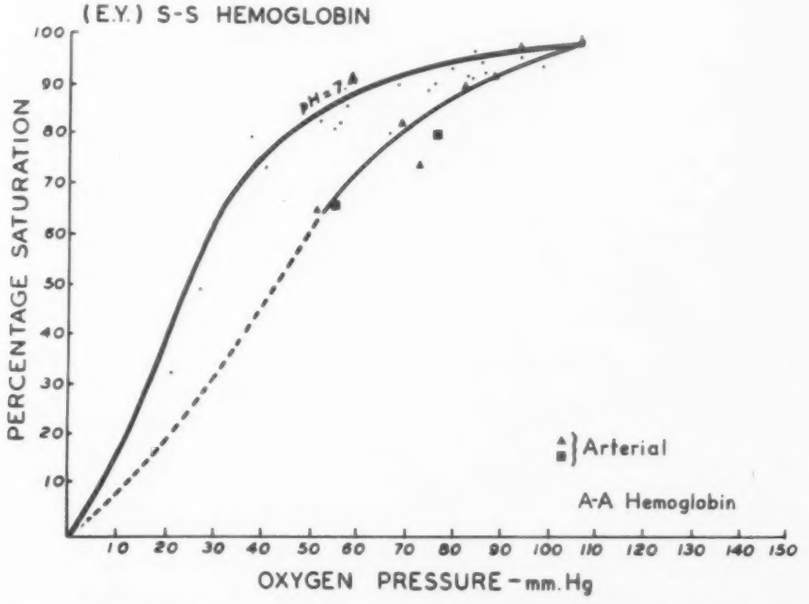


FIG. 3. Nine points on the dissociation curve of patient E. Y. with mild sickle cell anemia, together with the normal curve of Dill and the nineteen points determined in five subjects with A-A hemoglobin.

Although this curve is closer to the normal one than the curves of the other two patients with sickle cell anemia and appears to reach the normal curve at higher tensions, it is sufficiently displaced to result in arterial oxygen unsaturation at the usual partial pressures of oxygen in arterial blood.

Patient J. J. was restudied after being given 1,500 cc. of blood containing A-A hemoglobin which raised his hemoglobin content from 6.5 to

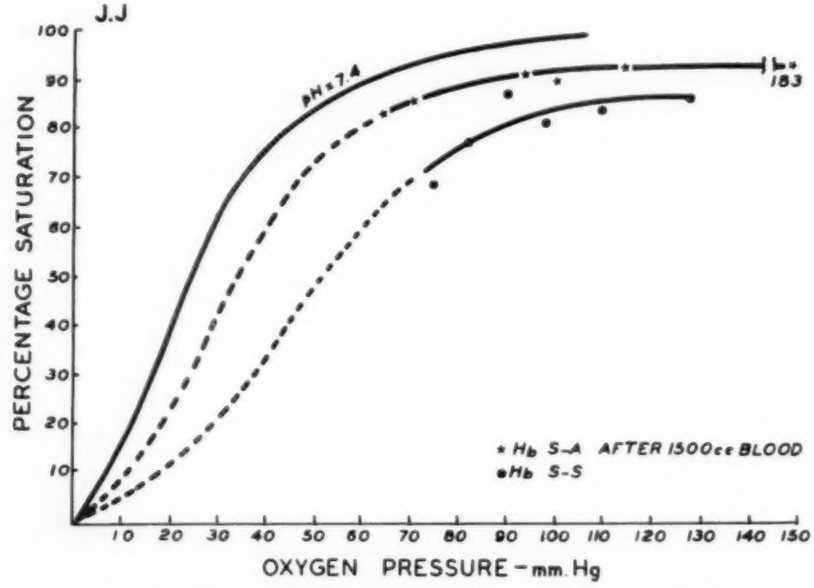


FIG. 4. The dissociation curve of patient J. J. (severe sickle cell anemia) before and after transfusion with 1,500 cc. of normal blood, showing marked displacement from the normal curve before transfusion with a shift toward normal after transfusion.

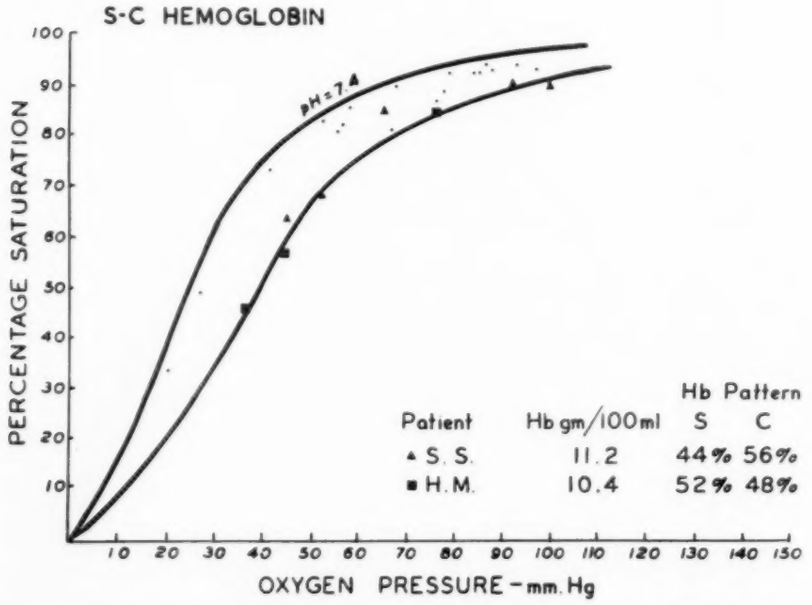


FIG. 5. Eight points on the dissociation curve of two patients with hemoglobin C-S disease, together with the normal curve of Dill and the nineteen points determined in five subjects with A-A hemoglobin.

11.5 gm. per 100 ml. and changed his electrophoretic pattern from 100 per cent S hemoglobin to 60 per cent S hemoglobin, 40 per cent A hemoglobin. The pre- and post-transfusion curves are plotted in Figure 4. The infusion of A hemoglobin shifted the curve toward the normal one.

Eight arterial points obtained on the two patients with C-S hemoglobin (S. S. and H. M.) are plotted in Figure 5 with the nineteen normal points for comparison. The dissociation curve drawn from these points, although not deviated as far as those of the patients with sickle cell anemia, is sufficiently displaced to account for

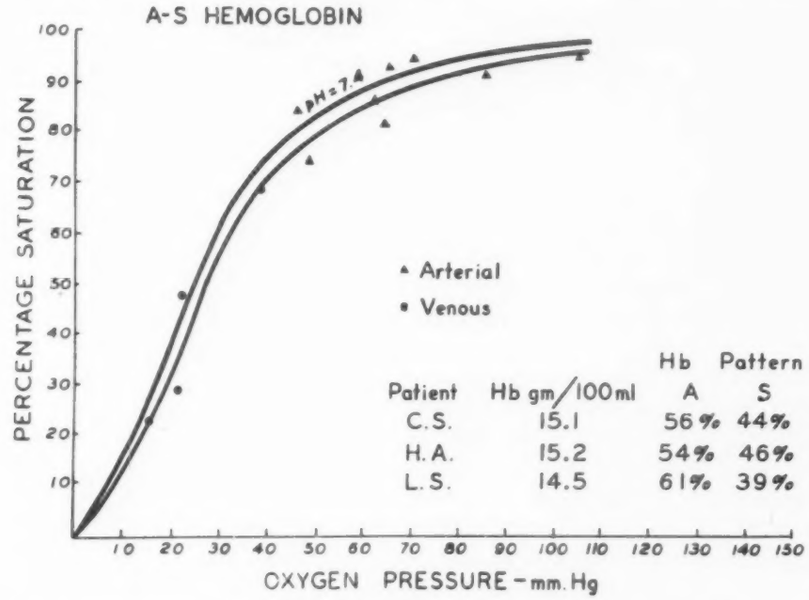


FIG. 6. Twelve points on the dissociation curve of three patients with A-S hemoglobin, together with the normal curve of Dill. The dissociation curve of the patients with A-S hemoglobin coincides with the curve determined in subjects with A-A hemoglobin in our laboratory.

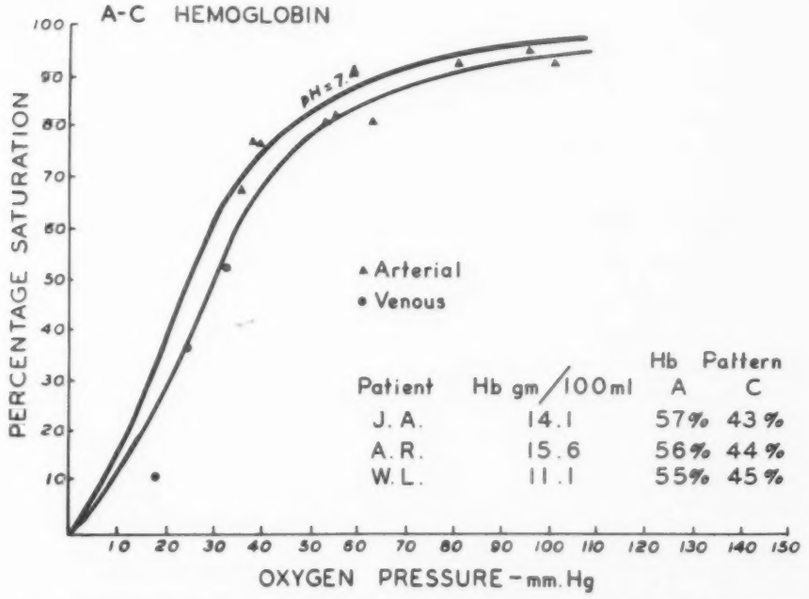


FIG. 7. Twelve points on the dissociation curve of three patients with A-C hemoglobin, together with the normal curve of Dill. The curve of these patients is not displaced from the curve of subjects with A-A hemoglobin.

the slight arterial oxygen unsaturation observed in these patients.

Although patient H. M. has an abnormal alveolar-arterial oxygen tension gradient (Table III), his arterial PO_2 (76 mm. Hg) corresponds to an arterial oxygen saturation of 93 per cent on the normal dissociation curve and would not account for the observed arterial oxygen saturation of 87.1 per cent.

Eight arterial and four venous points obtained on the three patients with A-S hemoglobin (C. S., H. A. and L. S.) are plotted in Figure

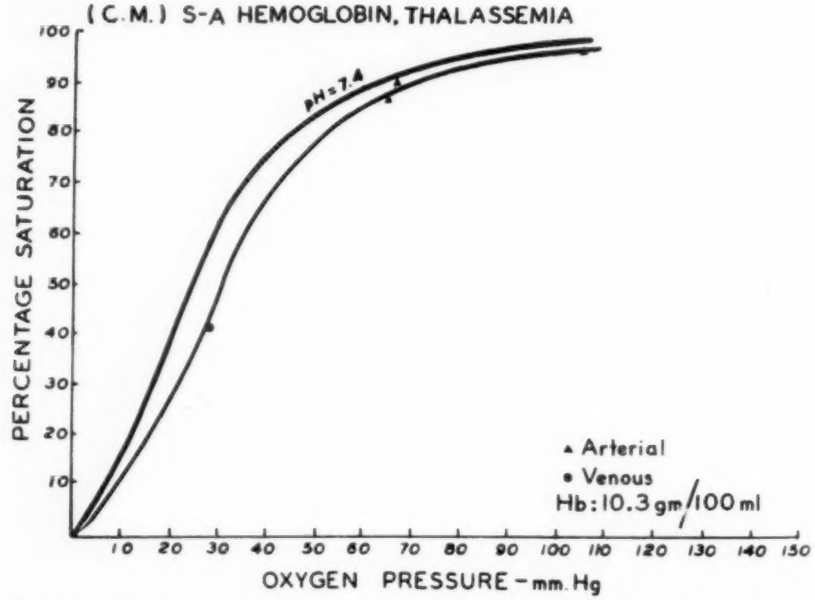


FIG. 8. Four points on the dissociation curve of patient C. M. (S-A, thalassemia), with the normal curve of Dill, demonstrating no significant displacement from the normal curve of our laboratory.

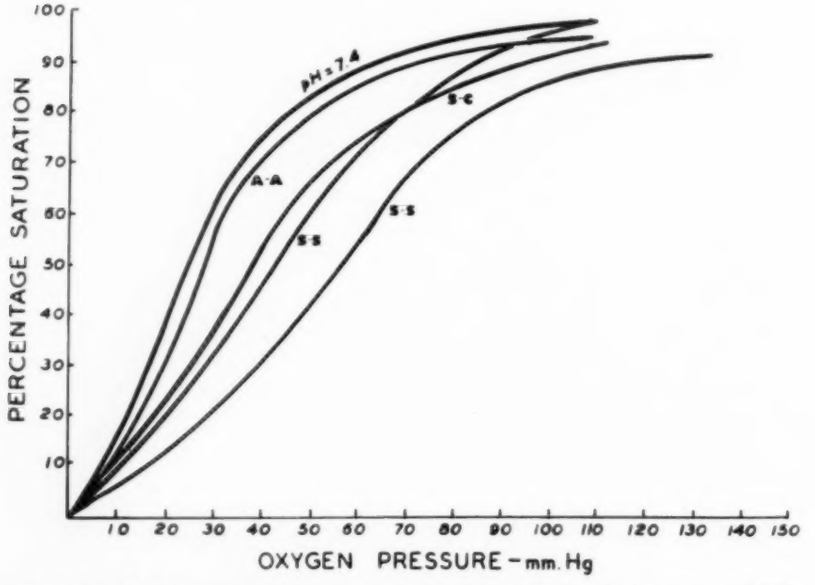


FIG. 9. Graphed for comparison are the normal *in vitro* dissociation curve of Dill, the normal (A-A hemoglobin) *in vivo* dissociation curve of our laboratory, the dissociation curve of a patient with hemoglobin C-S disease, the dissociation curve of a patient with mild sickle cell anemia, and the curve of a patient with severe sickle cell anemia.

6. There was no significant displacement of the curve plotted from these points and the arterial blood of these three patients was normally saturated with oxygen.

Nine arterial and three venous points obtained on the three patients with A-C hemoglobin (J. A., A. R. and M. L.) are plotted in Figure 7. The dissociation curve is normal in position and the arterial blood of these patients was normally saturated.

In Figure 8 are plotted three arterial and one venous point of patient C. M. who was classified as S-A thalassemia because of a 70 per cent S hemoglobin content and anemia. In spite of the

high content of abnormal hemoglobin the dissociation curve was not significantly displaced. An arterial oxygen saturation of 88.7 was present, however, on the basis of chronic pulmonary emphysema with a ventilation-perfusion defect, and increased alveolar to arterial gradient on 21 per cent oxygen. (Table III.)

All points except those determined on the dissociation curve of the three patients with sickle cell anemia were corrected to pH 7.40. It was believed that any correction based on the behavior of normal hemoglobin was not justified in the patients with sickle cell anemia. The observed pH's in these patients did not differ greatly from 7.40.

COMMENTS

Since pneumonitis and pulmonary infarction occur frequently in the sicklemic state, arterial oxygen unsaturation, when recognized, has generally been attributed to pulmonary insufficiency [*4*]. Although pulmonary dysfunction may be a factor in some patients, our data suggest that the unsaturation can best be explained by assuming that the abnormal hemoglobins have a reduced affinity for oxygen *in vivo*. This defect manifests itself as a displacement of the *in vivo* oxyhemoglobin dissociation curve to the right in patients whose red blood cells contain no A hemoglobin. The determination of several points on each patient permitted us to plot a large segment of the dissociation curve and establish that the magnitude of the displacement may be considerable. The degree of displacement was sufficient to explain the arterial oxygen unsaturation observed without invoking the presence of any pulmonary changes. The possibility of such a shift has previously been suggested by Becklake et al. [*5*] using *in vitro* tonometric technics and by Fowler, Smith and Greenfield [*6*] using both *in vitro* and *in vivo* technics.

Comparison of the dissociation curves of a patient with severe sickle cell anemia, one with mild sickle cell anemia, and one with hemoglobin C-S disease with the normal *in vivo* curve of our laboratory and the *in vitro* curve of Dill (Fig. 9), shows that the degree of displacement in this small group of patients seemed to correlate with the clinical severity of the disease; the more severe the disease, the greater the displacement.

Any attempt to explain the mechanism of the shift must be speculative at the present time. It would be convenient to attribute the shift to differences in the molecular properties of abnormal hemoglobin. Wyman and Allen [*7*], however, found that dialyzed sickle hemoglobin had the same dissociation curve as normal hemoglobin similarly prepared. The explanation must, therefore, lie in an alteration in the *in vivo* behavior of the hemoglobin. Changes in pH and temperature are the only factors known to alter the position of the oxyhemoglobin dissociation curve. A reduced pH of the red blood cell would be a reasonable explanation for the shift. Since no satisfactory method of measuring intracellular pH is available at the present time, this possibility cannot be verified experimentally. However some suggestive evidence of a reduced intracellular pH was observed. The pH of the blood containing only S hemoglobin, when subjected to continuous rotation to avoid settling, dropped rapidly following withdrawal from the blood vessel. This drop in pH (to about 7.20 in two hours) was accompanied by a slight drop in hematocrit due to hemolysis of the mechanically fragile sickle cells. If the blood were not subjected to continuous rotation, hemolysis did not occur and the pH remained stable. The drop in pH appeared to be greater than might be anticipated if the pH of the red cells were normal, and greater than that observed when a similar degree of mechanical hemolysis was induced in normal blood.

Displacement of the oxyhemoglobin dissociation curve to the right has been reported in anemias not due to hemoglobinopathies [*8–10*]. In an attempt to evaluate the role of anemia itself in the abnormal dissociation curve, patient J. J. was restudied after transfusion. His curve had shifted back toward normal (Fig. 4) after his hemoglobin content had been raised to 11.5 gm. per 100 ml. The correction of his anemia was accomplished, however, by the infusion of normal blood because of the hazard of administering abnormal hemoglobin to a patient with sickle cell anemia. The resultant curve is probably a summation of the curves of the two hemoglobin components, which behave independently because the S hemoglobin is contained in one group of red cells and the A hemoglobin in another. In patients with the sickling trait the red cells contain some of each type. A calculated curve based on the assumption of two independently acting hemoglobin components in concentrations present in this patient after transfusion coincides closely with the observed curve. Preliminary studies in our laboratory of anemic patients with normal

hemoglobin indicates that a shift in the dissociation curve occurs only when the hemoglobin content is less than 8 gm. per 100 ml. and that the magnitude of the shift is small when compared with that observed in patients with sickle cell anemia. We conclude, therefore, that the shift in the dissociation curve in sickle cell anemia is largely independent of the hemoglobin content.

It is of interest to note that patient J. J.'s dissociation curve was still markedly displaced (Fig. 4) following transfusion when his electrophoretic pattern was 60 per cent S, 40 per cent A. In contrast, patient C. M. (Fig. 8) had a normally placed curve with 70 per cent S hemoglobin. Patients H. M. and S. S. with hemoglobin C-S disease (Fig. 5) had abnormal curves with 52 per cent and 44 per cent S hemoglobin respectively. These findings suggest that the presence of only small amounts of A hemoglobin within the red cell preserve the normal affinity for oxygen. Only cells with entirely abnormal hemoglobin appear to have a reduced affinity for oxygen.

The clinical implications of a shift in the oxyhemoglobin dissociation curve depend upon the magnitude of the shift and the presence or absence of cardiopulmonary disease. If there is no associated cardiopulmonary dysfunction and the arterial oxygen tension is normal, a moderate shift of the dissociation curve will result in only slight arterial oxygen unsaturation because the upper portion of the curve is flat. At oxygen tensions that prevail in the tissues the curve descends steeply so that any rightward displacement will make oxygen more readily available to the cells. A moderate shift in the dissociation curve is, therefore, beneficial in anemia since it facilitates the transport of oxygen from the lungs to the tissues and thereby compensates, at least partially, for the hemoglobin deficit. If, however, the displacement is marked or if there is cardiopulmonary dysfunction severe enough to reduce the arterial oxygen tension significantly, marked arterial oxygen unsaturation will occur and tissue anoxia will be aggravated rather than ameliorated.

SUMMARY

The *in vivo* oxyhemoglobin dissociation curve has been studied in twelve patients whose hemoglobin was entirely or partially abnormal. Five had no normal hemoglobin. Three of these five had pure S hemoglobin and sickle cell anemia; two had hemoglobin C-S disease. Of the other 7 patients, 3 had A-S hemoglobin, three A-C hemoglobin and one S-A hemoglobin and thalassemia.

Arterial oxygen unsaturation was present in the five patients who had no normal hemoglobin and the oxyhemoglobin dissociation curve was displaced to the right. The degree of displacement was sufficient to explain the observed arterial oxygen unsaturation. The oxyhemoglobin dissociation curve was normal in patients with A-C and A-S hemoglobin and in the one patient with S-A hemoglobin and thalassemia.

It is suggested that displacement of the dissociation curve may be related to reduction of the intracellular pH of the red cell.

The clinical implications are briefly discussed. A moderate shift of the curve is beneficial in anemia if cardiopulmonary function is normal. A marked shift, however, or even a moderate shift in the presence of significant cardiopulmonary dysfunction, will aggravate the tissue anoxia of the anemic state.

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The Paradox of the Antibody Response to Streptodornase*

The Usefulness of Antidesoxyribonuclease B as an Indication of Streptococcal Infection in Patients with Acute Rheumatic Fever

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TESTS for neutralizing antibody to streptococcal desoxyribonuclease (streptodornase, streptococcal Dnase) have been considered a poor index of preceding streptococcal infection in patients with acute rheumatic fever because of the relative infrequency with which antibody to this enzyme appears to develop [*1*]. It is indeed paradoxical that an antibody response to this enzyme has been demonstrated in so few patients with streptococcal infections since desoxyribonuclease activity is produced by virtually all strains of group A streptococci in large amounts and under a variety of culture conditions [*2*].

The recent observation [*3*] that group A streptococci can produce three serologically distinct desoxyribonucleases, designated A, B and C, has resulted in a reasonable explanation for this paradox. This paper will present data on the frequency and magnitude of development of neutralizing antibody to these three enzymes following streptococcal infections in patients and will demonstrate that antibody to one of these (desoxyribonuclease B) develops often enough and in sufficient titers to make it a useful test in patients with acute rheumatic fever.

METHODS

Strains of Group A Streptococci. Strain H 105 Op is an opaque variant of Tillett's "CO." This strain is an undesignated new type producing high yields of streptokinase and, under the culture conditions of this study, produces predominantly Dnase A; in certain circumstances this strain will also produce significant amounts of Dnase B.

Strain Dematteo is a type 12 streptococcus isolated from a patient with acute glomerulonephritis (supplied by Dr. Charles H. Rammelkamp, Jr.). Under the culture conditions of this study, this strain produces predominantly Dnase B.

Strain 1 GL 88 is a type 17 streptococcus isolated at the Great Lakes Naval Station from a patient with scarlet fever who subsequently developed acute rheumatic fever (obtained from Dr. Rebecca Lancefield). Under the culture conditions of this study, this strain is a relatively good producer of Dnase C, but also produces large amounts of Dnase B.

Culture Methods and Preparation of Enzymes. Group A streptococci were grown in a dialysate medium of casamino acids, Pfanstiehl peptone, "R. I." and beef heart infusion [*4*]. The extracellular products in the supernatant fluid were concentrated by precipitation with ammonium sulfate and by filtration through a collodion bag [*4*]. The three desoxyribonucleases migrate distinctly under these conditions [*3*], and electrophoretic fractions representing the three enzymes A, B and C were used in the antibody neutralization tests.

By proper choice of strain, it was sometimes possible to select group A streptococci which under these culture conditions produce predominantly one of the three enzymes and negligible amounts of the other two. The unconcentrated and unfractionated supernate of these strains was found to yield results similar to those obtained with the electrophoretically separated fractions. This greatly simplified the problem of obtaining suitable enzyme preparations. Strain Dematteo can be used in this way for production of suitable supernates containing predominantly Dnase

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† Career Investigator of the American Heart Association.

TABLE 1
VARIATION IN NEUTRALIZATION OF SPECIFIC STREPTOCOCCAL DESOXYRIBONUCLEASES BY HUMAN SERUMS

No. of Patient	Antidesoxyribonuclease Titer (reciprocal of dilution)		
	A Enzyme	B Enzyme	C Enzyme
H-156	320	20	<10
GL 23	<10	2560	<10
W 68	<10	40	160

B. Strain H 105 Op will usually produce Dnase A in sufficient excess for these purposes but will sometimes produce significant amounts of Dnase B. Strain 1 GL 88 is the best producer of Dnase C identified to date, but this strain also produces large amounts of Dnase B, which makes crude supernates of this strain unsuitable for use in distinguishing specific neutralizing antibodies.

Serums. Serum specimens were obtained from patients and normal laboratory personnel at the Hospital of the Rockefeller Institute for Medical Research, and from patients at the Great Lakes Naval Station, Chicago, Illinois, the Streptococcal Diseases Laboratory, F. E. Warren Air Force Base, Cheyenne, Wyoming, and the University of Minnesota Hospitals.

Serums were obtained from forty-one patients with acute rheumatic fever and from fifty "non-rheumatics" who had no history of recent streptococcal infection, rheumatic fever, or acute nephritis. This latter group was composed of forty-five patients with other illnesses and of five laboratory personnel. The ages of the patients with acute rheumatic fever ranged from five to twenty-seven years with a mean age of 16.4 years. The ages of the non-rheumatic group ranged from five to thirty-five years with a mean age of 16.0 years.

Paired serums were examined from fifty-seven patients with untreated streptococcal infections. All patients had exudative pharyngitis or tonsillitis and were harboring group A streptococci at the time the acute serum specimen was obtained. The convalescent serum specimen was obtained after an interval of approximately three weeks. In order to increase the comparability of test conditions, the acute and convalescent serums of a pair were examined on the same day. One or more standard serums were included as controls in each set of serums examined.

Antistreptolysin O titers were estimated by the Hodge-Swift method [5] or a modification of this method using serum dilutions in 0.1 log increments. Antistreptolysin O titers were performed at the Streptococcal Diseases Laboratory and at the Rockefeller Institute.

Measurement of Neutralizing Antibodies for the Desoxyribonucleases. Antiserums were tested for neutralizing antibody by the alcohol precipitation test of McCarty [1]. Substrate solution contained 0.1 per cent sodium desoxyribonucleate prepared from calf thymus [1] and 0.01 M $MgSO_4$ in 0.025 veronal buffer, pH 7.7. The sodium desoxyribonucleate was first dissolved in distilled water by allowing to stand overnight at 4°C. The following day a solution of $MgSO_4$ and veronal buffer was added in appropriate strength to achieve the desired final concentration of the various ingredients. Chloroform (0.7 per cent) was added to prevent contamination. The substrate solution usually remained stable for several days to several weeks at 4°C. but was tested before using to ascertain that a suitable fibrous precipitate formed upon the addition of ethyl alcohol. Both serum and enzyme dilutions were made in neopeptone dialysate [6] to which 0.7 per cent chloroform had been added to prevent contamination.

The appropriate dilution of the specific enzyme preparation to be used was determined as follows: Serial dilutions of the enzyme preparation were made in neopeptone dialysate, and 0.25 ml. of each dilution was mixed with 0.25 ml. of neopeptone dialysate and 0.5 ml. of substrate solution. After thirty minutes at 37°C., 1 ml. of ethyl alcohol was added. The highest dilution of enzyme degrading the sodium desoxyribonucleate to the point at which no fibrous precipitate formed was determined, and a concentration equivalent to four times this amount was used in the test for antibody neutralization.

All serums were heated at 65°C. for thirty minutes to destroy or reduce intrinsic serum nuclease activity. Inactivation can be conveniently achieved by heating the initial 1:10 dilution in neopeptone dialysate. Serums were diluted in neopeptone dialysate in serial twofold dilutions, beginning at 1:10, or for more precise titration in 0.1 or 0.2 log dilutions. For measuring antibody neutralization, 0.25 ml. of each dilution of serum was mixed with 0.25 ml. of the appropriate dilution of enzyme, and then the mixture was incubated at 37°C. for thirty minutes. Substrate solution, 0.5 ml., was added and the incubation was continued for another thirty minutes. One ml. of ethyl alcohol was added and the tube was agitated. The end point was defined as the highest serum dilution which inhibited enzyme activity so that a definite fibrous precipitate appeared in the presence of alcohol.

RESULTS

Considerable variation was often noted in the ability of a given human serum to neutralize the three specific desoxyribonucleases. Examples of such variations are presented in Table 1. Furthermore, in individual patients differences

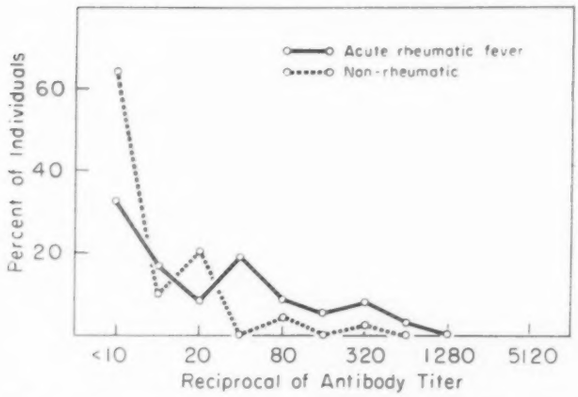


FIG. 1. Per cent distribution of antibody titers for Dnase A among persons with and among those without acute rheumatic fever.

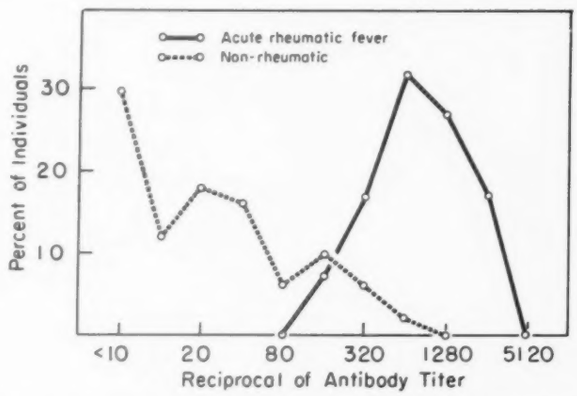


FIG. 2. Per cent distribution of antibody titers for Dnase B among persons with and among those without acute rheumatic fever.

in antibody response to the specific desoxyribonucleases occurred following streptococcal infection. Table II lists examples in which an antibody response to one enzyme was demonstrated when no response was shown to the other two enzymes. These data support previous observations that Dnases A, B and C are serologically distinct [*3*].

A comparison of the antibody titers for the three enzymes in forty-one patients with and in fifty persons without acute rheumatic fever is given in Figures 1 to 3. These figures present the per cent distribution of persons in the two groups according to antibody titer for each specific enzyme. Four patients with acute rheumatic fever have been omitted from Figures 1 and 3, and five subjects without this disease have been omitted from Figure 3 because of insufficient serums to complete antibody studies. The data as presented here are essentially the same as when these subjects are omitted from all figures.

Antibody titers for Dnases A and C were low in persons without acute rheumatic fever. (Figs. 1 and 3.) In more than 60 per cent of these subjects, no antibody could be demonstrated to Dnase A and in more than 85 per cent no antibody was found to Dnase C. Antibody titers of 1:80 or greater for Dnase A were observed in exceptional persons without acute rheumatic fever (about 5 per cent), but no titers above 1:20 were found for Dnase C in this group.

Patients with acute rheumatic fever tended to show somewhat higher antibody titers for Dnases A and C than did those without the disease as illustrated by the slight shift to the right of the distribution of rheumatic patients in Figures 1 and 3. Fewer patients with acute rheumatic fever showed an absence of antibody to these two enzymes. In addition, approximately 40 per cent of patients with acute

TABLE II

VARIATION IN ANTIBODY RESPONSE TO SPECIFIC DESOXYRIBONUCLEASES FOLLOWING STREPTOCOCCAL INFECTIONS

No. of Patient	Antidesoxyribonuclease Response (log increment in titer)*		
	A Enzyme	B Enzyme	C Enzyme
W 7	0.5	0	0
W 39	0	1.5	0
W 51	0	0	0.3

* An increment of 0.2 log is reproducible and therefore considered "significant."

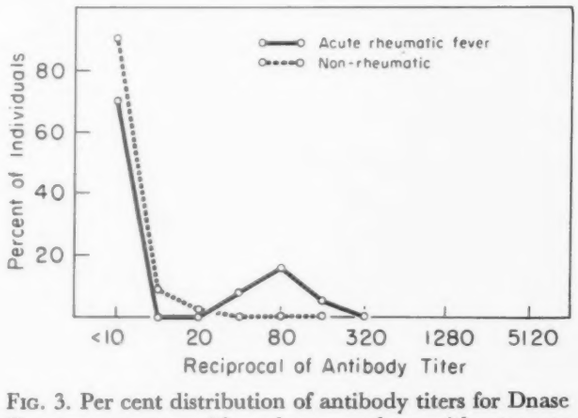


FIG. 3. Per cent distribution of antibody titers for Dnase C among persons with and among those without acute rheumatic fever.

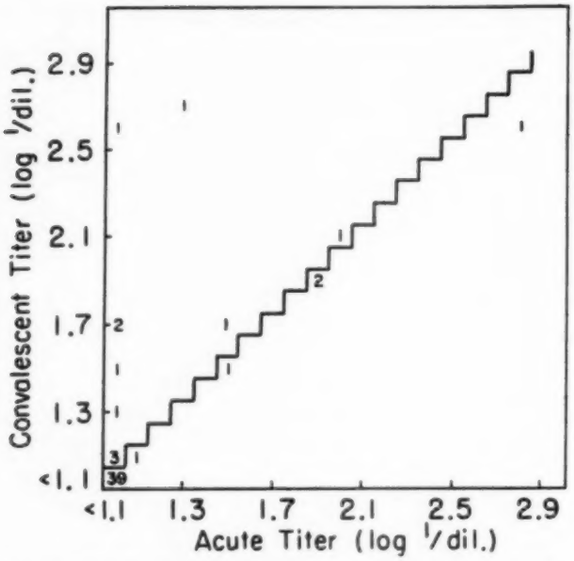


FIG. 4. Distribution of acute and convalescent antibody titers for Dnase A among patients with streptococcal infections. (Figures refer to number of patients. Figures above the diagonal line indicate patients whose serums showed an increase in titer.)

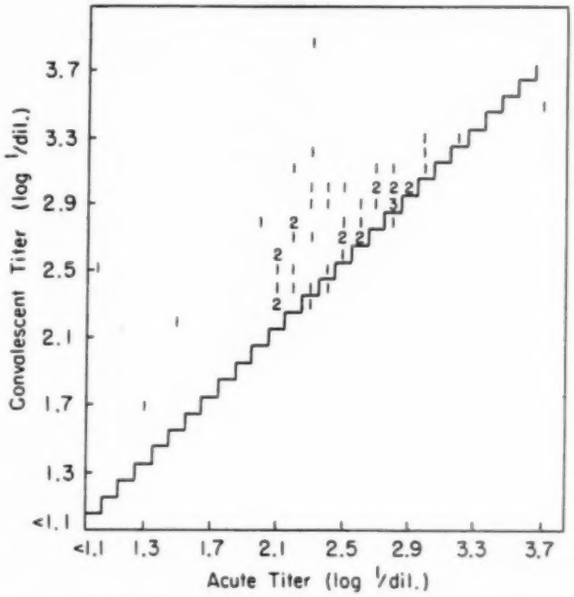


FIG. 5. Distribution of acute and convalescent antibody titers for Dnase B among patients with streptococcal infections. (Fig. 4.)

rheumatic fever showed antibody titers of 1:40 or greater for Dnase A, and approximately 30 per cent of patients with acute rheumatic fever showed antibody titers of this magnitude for Dnase C.

In contrast to the relatively slight difference between the rheumatic group and the group without acute rheumatic fever in regard to titers of anti-Dnases A and C, a marked shift to the higher titers on the right was noted in the distribution of anti-Dnase B titers among patients with acute rheumatic fever (Fig. 2). Antibody titers for this enzyme were considerably higher than those for Dnases A and C, ranging from 1:160 to 1:2560 in patients with acute rheumatic fever. Among those without the disease, antibody titers for Dnase B also tended to be higher than those for the other two enzymes. Only 30 per cent of these persons had no demonstrable antibody to Dnase B, whereas 60 per cent or more had titers in the 1:10 to 1:160 range. However, the extent of overlapping of the non-rheumatic and rheumatic groups is relatively slight for anti-Dnase B since less than 10 per cent of persons without acute rheumatic fever had antibody titers of 1:320 or greater whereas more than 90 per cent of patients with acute rheumatic fever demonstrated titers of 1:320 or greater.

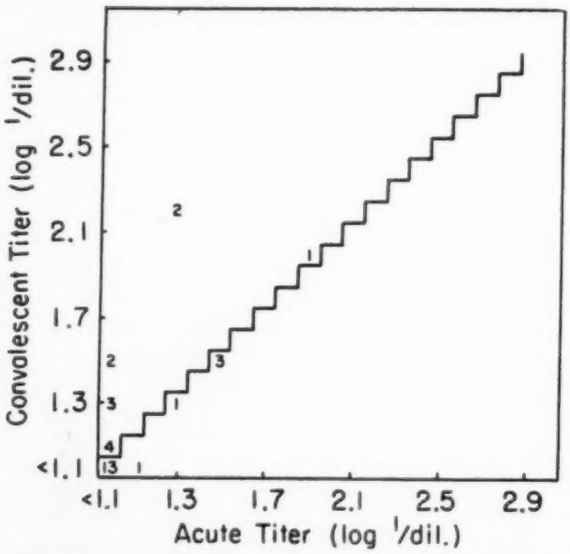


FIG. 6. Distribution of acute and convalescent antibody titers for Dnase C among patients with streptococcal infections. (Fig. 4.)

The demonstration of antibody to Dnase B in high titers in patients with acute rheumatic fever and in low titers among many persons without the disease suggests that this is a common antigen among strains of group A streptococci. In contrast, the relative infrequency of demonstrable antibody to Dnases A and C, among both rheumatic and non-rheumatic groups, suggests that these are antigens which are less prevalent among group A streptococci.

TABLE III

ANTIBODY RESPONSE FOLLOWING STREPTOCOCCAL INFECTION ACCORDING TO SEROLOGICAL TYPE OF INFECTING ORGANISM

Serological Type of Infecting Streptococcus	No. of Patients											
	Anti-Dnase A Response*				Anti-Dnase B Response*				Anti-Dnase C Response*			
	No Rise	0.1 Log	0.2 Log or >	Total	No Rise	0.1 Log	0.2 Log or >	Total	No Rise	0.1 Log	0.2 Log or >	Total
1	4	..	..	4	1	1	2	4	2	1	1	4
3	3	..	2	5	..	1	4	5	..	..	..	..
5	4	1	2	7	1	..	7	8	3	2	3	8
6	1	..	..	1	..	1	..	1	1	..	..	1
12	2	1	..	3	..	1	2	3	3	..	..	3
14	13	1	1	15	1	3	10	14	4	2	2	8
18	3	..	..	3	..	1	2	3	2	..	1	3
19	6	..	..	6	..	3	2	5	..	..	..	..
28	1	2	1	4	1	..	4	5	3	..	..	3
30	7	..	..	7	..	1	5	6	..	..	..	..
Total	44	5	6	55	4	12	38	54	18	5	7	30

* Increment between acute and convalescent titers.

These conclusions are supported by further studies of the frequency of antibody response to the three desoxyribonucleases following streptococcal infection. (Figs. 4 to 6.) For these studies the antibody change in acute and convalescent serums was determined, using dilutions of 0.2 log increment from 1:12.5 to 1:50 and of 0.1 log increment above 1:50. A total of fifty-seven patients was studied. Sufficient serum was available to study the antibody response to Dnase A in fifty-five patients, to Dnase B in fifty-four patients and to Dnase C in thirty patients.

In about 85 per cent of acute serums examined, no antibody to Dnase A was demonstrable. (Fig. 4.) Furthermore, only approximately 12 per cent of patients showed an 0.2 log or greater antibody response to this enzyme following streptococcal infection, although exceptional patients showed increases of more than 1 log.

With only one exception, all acute serums studied showed measurable antibody to Dnase B. (Fig. 5.) This is in agreement with the previous finding of antibody to Dnase B in low titers among persons without the disease. (Fig. 2.) However, the median acute antibody titer for this enzyme is higher for the group in Figure 5 than for the non-rheumatic group in Figure 2. Although slightly higher antibody titers might be expected when serums are examined by dilutions at closer intervals, it is likely that the explanation for high acute titers in this group also lies in the nature of the group examined. These serums were obtained from a military population of young adult men who were stationed in an area of epidemic streptococcal disease, and it is probable that many of them had had previous streptococcal infections, some within the recent past.

The regularity with which an antibody response to Dnase B occurs following streptococcal infection is illustrated in Figure 5. In 70 per cent of patients an increase of 0.2 log or greater was found and in another 22 per cent a rise of 0.1 log was demonstrated. Only four of fifty-four patients (less than 8 per cent) failed to show a rise.

Previous studies of antistreptolysin O response [*7,8*] have indicated that, because of the mechanics of serial dilutions commonly employed, a "significant" response (two or more dilution tubes) is less frequently demonstrated when acute titers are high. Consequently, one would expect fewer "significant" responses in a group in which the initial antibody titer is generally high. This observation also appears to apply to

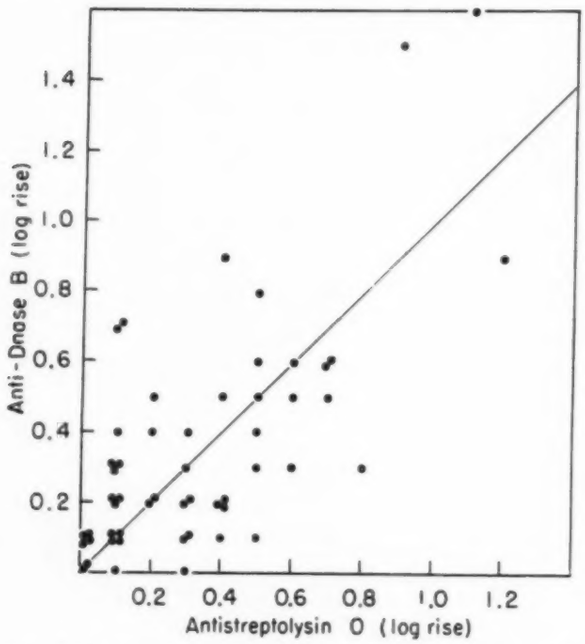


FIG. 7. Comparison of antistreptolysin O response and anti-Danse B response in patients following streptococcal infections. Responses compared are the increments between acute and convalescent antibody titers (log rise) for this particular streptococcal antigen.

antibody responses to Dnase B since rises of 0.2 log or more (two or more dilution tubes) occur less frequently among those persons with high initial titers. (Fig. 5.) It is possible that rises of 0.1 log (one dilution tube) are more likely to be of real significance when the acute titer is elevated than when it is low.

Since earlier studies [*3*] had suggested that the kind and amounts of the three desoxyribonucleases produced varies among the strains of group A streptococci, the antibody response to these individual enzymes was studied according to the infecting serological type of streptococcus. The data in Figures 4 to 6 analyzed according to the type of streptococcus isolated during the acute infection are presented in Table III. Ten serological types were identified but the numbers in each group are necessarily small. An anti-Dnase B response almost always occurred regardless of the infecting type. This supports the previous conclusion that this antigen must be produced by most group A streptococci. Antibody responses to Dnase A and to Dnase C were observed following infections with some types and not with others, but the data are too few to establish a definite type relationship. These antigens are probably less common than Dnase B. However, the presence

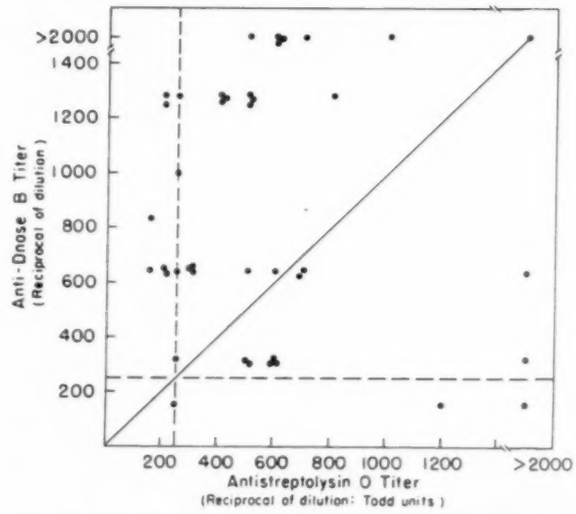


FIG. 8. Comparison of antistreptolysin O titers and anti-Dnase B titers in patients with acute rheumatic fever.

or absence of a response in any given situation may be related not only to the antigenic composition of the products of the infecting strain but also to previous exposure to this antigen.

A comparison of the anti-Dnase B response with the antistreptolysin O response following streptococcal infection is presented in Figure 7. Except for one patient omitted because of insufficient serum for antistreptolysin O titer, the patients are the same as those presented in Figure 5. Identical dilution increments (0.1 log) were employed for both antibody tests. In this figure each dot represents a single patient; its location indicates the increase in titer of one antibody relative to that of the other.

In Figure 7 the dots are about equally distributed on each side of the diagonal line, indicating that in approximately half of the patients the antistreptolysin O response was greater and in the other half the anti-Dnase B response was of greater logarithmic magnitude. Six patients failed to show an antistreptolysin O response, and four patients failed to show an anti-Dnase B response. Two patients failed to show a response to either antigen. Fourteen patients showed an antistreptolysin O response of only 0.1 log and twelve patients showed an anti-Dnase B response of only 0.1 log. Therefore, it appears that anti-Dnase B compares favorably with antistreptolysin O both in frequency and magnitude of response.

As shown in Figure 7, and as previously noted [*1*], individual patients may show wide variations in their antibody response to various

streptococcal antigens. This variation emphasizes the advantage of studying several different antibodies when looking for evidence of a recent streptococcal infection. For example, in Figure 7, of the twenty patients who failed to show a rise of 0.2 log or greater for antistreptolysin O, nine (or 45 per cent) showed a 0.2 log rise for anti-Dnase B. Similarly, of the sixteen patients who failed to demonstrate an increase of 0.2 log or greater for anti-Dnase B, five patients (or 31 per cent) showed an 0.2 log rise for antistreptolysin O.

Titers of anti-Dnase B and of antistreptolysin O in patients with acute rheumatic fever are compared in Figure 8. The patients presented here are the same as those included in Figure 2. In contrast to the preceding figure (Fig. 7), which compared the antibody rises for the two antigens in patients with streptococcal infections, Figure 8 compares single admission titers in patients with acute rheumatic fever.

In general, anti-Dnase B titers were higher than antistreptolysin O titers in patients with acute rheumatic fever (68 per cent). Six patients showed antistreptolysin O titers of less than 1:250 (250 Todd units), whereas only three patients showed anti-Dnase B titers of less than 1:250. Furthermore, most anti-Dnase B titers were well above this level. The frequency of high levels of anti-Dnase B in patients with acute rheumatic fever makes its reliability as an indicator of recent streptococcal infection comparable to that of the antistreptolysin O test. Moreover, nearly all patients with low or borderline antistreptolysin O titers showed anti-Dnase B titers which were unquestionably elevated.

Although different dilution schemes were employed for the two antibodies presented in Figure 8, this should not greatly affect the results. If dilutions at closer intervals had been employed for the anti-Dnase B test, slightly higher values would be expected.

COMMENTS

Two paradoxes in the immunological response to streptococcal infections have been described [*1,9*]. One concerns hyaluronidase. Neutralizing antibody for this enzyme has been observed in many patients following streptococcal infection, and without regard to infecting type, although only a few strains of group A streptococci (types 4 and 22) produce appreciable amounts of hyaluronidase *in vitro*. A paradox of the reverse sort has been noted in regard to streptococcal desoxyribonuclease (streptodornase). Despite the large amounts of desoxyribonuclease produced by virtually all strains of group A streptococci, neutralizing antibody has been demonstrated in relatively few patients following streptococcal infection and low titers have often been noted in patients with acute rheumatic fever.

Several explanations may be considered for the infrequency with which antibody to desoxyribonuclease was demonstrated in previous studies. Desoxyribonuclease may be a poor antigen [*10*]. No direct support for this thesis has been obtained in experimental animals since immunization can be achieved without unusual difficulty [*1,3*]. Another possible explanation is that antidesoxyribonuclease is unstable and therefore disappears more rapidly from the body than other streptococcal antibodies [*1*]. However, in patients followed for many months after scarlet fever the rate of decrease of antidesoxyribonuclease titer was comparable to that of other streptococcal antibodies [*1*].

A third possible explanation is that group A streptococci can produce more than one desoxyribonuclease and that these enzymes are immunologically distinct. Direct evidence for this possibility has been presented in an earlier paper [*3*], in which it was demonstrated that group A streptococci can produce three serologically distinct desoxyribonucleases designated streptococcal Dnases A, B and C. The present paper presents additional evidence that following natural infection the antibody response to each of these enzymes is independent.

In previous antibody studies for streptococcal desoxyribonuclease, a strain of group A streptococcus (H 105 Op) has been employed which produces primarily Dnase A. However, the present studies indicate that antibody responses to this enzyme occur infrequently, apparently because this is an uncommon antigen among strains of group A streptococci. It is therefore not surprising that earlier studies demonstrated an antidesoxyribonuclease response in relatively few patients.

In contrast to the rather disappointing and paradoxical results of previous studies, the present report indicates that when antibody to the more common antigen, Dnase B, is specifically tested for, it can be shown to develop regularly and in high titers following streptococcal infection. Therefore, the presence of neutralizing antibody to this new enzyme,

Dnase B, would appear to be a useful indicator of preceding streptococcal infection in patients with acute rheumatic fever, and probably also in patients with acute nephritis [*11*].

Anti-Dnase B compares favorably with antistreptolysin O, both in frequency and magnitude of response following streptococcal infection and in the level of titers observed in patients with acute rheumatic fever. Although in some respects this new antibody test appears to be slightly better, it is not likely that the anti-Dnase B test will displace the antistreptolysin O test which is widely accepted and well standardized.

However, an appreciable number of patients with acute rheumatic fever have low or borderline antistreptolysin O titers, and the anti-Dnase B test would appear to be particularly useful in such patients. In the patients reported here with questionably elevated antistreptolysin O titers, the anti-Dnase B titer was almost always definitely elevated.

The anti-Dnase B test has certain advantages over other streptococcal antibody tests, such as tests for antihyaluronidase and antistreptokinase which have been used as secondary tests in the past. The frequency of antibody response to Dnase B is very high. The alcohol precipitation test is reproducible and is easy to standardize and to perform. Substrate may be prepared in the laboratory [*1*] or obtained commercially, but only highly polymerized preparations are satisfactory. The availability of strains which produce large amounts of Dnase B and negligible amounts of the other two desoxyribonucleases obviates the necessity for using electrophoretically separated enzyme preparations; with suitable strains, the unfractionated broth culture supernate may be used as a source of enzyme for the antibody test.

SUMMARY

The paradoxical infrequency with which an antibody response to streptococcal desoxyribonuclease (streptodornase, Dnase) has been noted to develop following streptococcal infection can be explained by the demonstration of three immunologically distinct desoxyribonucleases, designated streptococcal Dnases A, B and C. Antibody responses to Dnases A and C occur rarely, whereas antibody responses to the more common antigen, Dnase B, occur regularly following streptococcal infection. The frequency and magnitude of the antibody response to Dnase B make it comparable to the antistreptolysin O test as a reliable indicator of recent streptococcal infection in patients in whom the diagnosis of acute rheumatic fever is being considered. The anti-Dnase B test is particularly useful in patients with acute rheumatic fever who present with low or borderline antistreptolysin O titers. In such patients the anti-Dnase B titer is often unquestionably elevated.

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Disturbances of Digestive Physiology Following Acute Drinking Episodes in "Skid-Row" Alcoholics*

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WHEN the "skid-row" alcoholic becomes so sick that another drink does not relieve his symptoms of nausea, vomiting and abdominal distress, he usually terminates his drinking spree and seeks medical attention. If he shows overt signs of the serious complications of alcoholism such as jaundice or other stigmas of decompensated hepatic disease, delirium tremens, acute pancreatitis, hemorrhagic gastritis or acute complications of peptic ulceration, he is likely, in Boston, to be admitted to the Boston City Hospital. In the absence of such overt disease he presents himself voluntarily for admission to the Long Island Hospital, the Chronic Diseases Division of the Boston City Hospital.

Of the numerous symptoms produced by excessive drinking the most commonly noted are disturbances of the digestive tract. As these digestive symptoms may herald more serious disorders of the digestive system, a study of the functional state of the digestive tract of chronic alcoholic patients was undertaken.

MATERIALS AND METHODS

The large number of alcoholic patient admissions (approximately 1,000) per year at the Long Island Hospital make it ideally suited for an intake study of the skid-row alcoholic.

A total of 471 admissions (admissions will henceforth be considered patients) of skid-row alcoholics were studied. All these patients were admitted within twelve hours of their last drink, terminating an alcoholic episode of one to sixteen weeks' duration. The first 336 consecutive patients were admitted between June and September, 1955. The remaining 135 patients (135 admissions of 126 patients 36 of whom were included in the previous series) were selected from 600 patients admitted between October 1955 and May 1956. Those patients who sought admission to escape the rigors of a New England winter were excluded.

The age of the patients ranged from twenty-four to sixty-two years (average: forty-three years), and they had been drinking heavily for an average of twenty years. A typical day's intake consisted of one-fifth (⅕ gallon) of "whiskey," ten to twenty 10-ounce glasses of beer or an equivalent amount of wine. Beverages consumed included, in addition to those mentioned, "canned heat" (Sterno®), shaving lotion, Jamaica ginger, vanilla extract, denatured alcohol, isopropyl alcohol, various medicinal elixirs such as terpin hydrate and codeine, astringents, antifreeze and liquid shoe polish.

Complaints on admission included nausea, vomiting, "dry heaves," abdominal distress nervousness, extreme excitability, "shakes," weakness, fatigue and general malaise. Further, many of the patients admitted during the winter had complaints related to acute and chronic respiratory diseases including tuberculosis; these patients were excluded from the study.

Although histories were obtained from all patients on admission only those admitted to the alcoholic patients' ward were available for verification by repeat questioning, so that an attempt to quantitate complaints was made on the latter group only. Histories taken from these patients revealed the following: none of the group had had a prior diagnosis of cirrhosis; one patient had a history of infectious hepatitis; thirty-two patients had histories of extreme dyspepsia including morning retching, nausea and vomiting; four patients had had gastrointestinal bleeding (see Table 1), one had had a perforated gastric ulcer and seven had a history of duodenal ulcers confirmed by x-ray examination or surgery. Eighteen patients complained of frequent diarrhea and four claimed chronic constipation.

* From the Long Island Hospital, the Gastro-intestinal Research Laboratory of the Mallory Institute of Pathology, Boston City Hospital, and the Department of Pathology, Boston University School of Medicine, Boston, Massachusetts. This investigation was supported in part by grants from the Ames Company, E. R. Squibb Co., the U. S. Public Health Service, the American Cancer Society (New York) and the Damon Runyon Memorial Fund.

TABLE I
CORRELATION BETWEEN GASTRIC TESTS AND PATHOLOGY

Pathologic Conditions	Verification	Tests			
		On Admission		Repeat	
		Diagnex*	Uropepsin	Diagnex	Uropepsin
Gastritis and duodenitis	History, hematemesis, melena	143	3,276	...	.....
Gastritis	History, hematemesis	18	2,930	20	7,824
???	No history, hematemesis	29	10,624	...	.....
Duodenal ulcer	Roentgenogram	18	1,070	...	.....
Duodenal ulcer	Roentgenogram	90	1,408	112	576
Duodenal ulcer	Roentgenogram, hematemesis	...	2,000	...	2,000
Duodenal ulcer	Roentgenogram	30	15,780	...	.....
Duodenal ulcer	Roentgenogram	305	4,800	136	3,884
Duodenal ulcer	Surgery (gastrectomy) ? hematemesis	21	.....	...	.....
Duodenal ulcer	Surgery (gastrectomy, recent) ? hemorrhage	58	1,858	58	4,480
Gastric ulcer	Surgery (gastrectomy, recent)	60	1,700	...	.....

* .3 mg. of Azure A = Klett reading of *80*. (Readings are in Klett units.)

PROCEDURE

On admission routine physical examinations were made on all patients, after which samples of urine were collected, blood drawn and, in some cases, gastric intubation performed. Studies were made of the functional state of the liver, biliary tract and gallbladder, pancreas and gastrointestinal tract. (Table II.) Patients who were studied by special tests, such as iodine absorption, vitamin A tolerance test, xylose tolerance test, Graham Cole series or tubeless gastric analysis were not permitted to ingest any food orally after the evening meal. The iodine absorption test was performed after fourteen to sixteen hours of fasting; the other tests were conducted following an overnight fast. When the patients had recovered from the acute effects of their alcoholic bout, as evidenced by marked weight gain and general physical improvement, they were notified to report for re-examination. The usual time lapse between admission and this re-examination was approximately two weeks. As the population was a transient one, adequate follow-up studies were most difficult to obtain.

RESULTS

Physical Findings. General: The patients appeared moderately to well nourished, with evidence of dehydration. They were usually tremulous and many were agitated, confused and partially disoriented: only four patients showed marked evidence of wasting. Most patients had a rapid pulse (100 to 120 per minute), shallow and rapid respirations, low to normal blood pressure (100 to 110/70 mm. Hg). Patients with temperature elevation above 99°F. were excluded. Upper abdominal tenderness was an almost universal finding. Forty-three of 115 patients examined for hepatomegaly had non-palpable livers, seventy-two had some degree of enlargement. Thirty-eight of the patients in this latter group had a liver edge extending 3 cm. or less below the right costal margin while in the remaining thirty-four patients, the liver edge was palpated more than 3 cm. below the costal margin. Two patients had clinical evidence of cirrhosis, including capillary telangiectasis, palmar erythema, collateral circulation and ascites. One additional patient had ascites (this patient left the hospital before the cause of his ascites could be ascertained). Sigmoidoscopy was performed in fourteen patients. Superficial erythema, increased mucosal friability with petechiae, easy bleeding and an excessive mucous secretion was noted in eleven patients, one of whom also had hemorrhoids. One case of rectal prolapse was seen and one case of frank ulcerative colitis was found.

Gastrointestinal Function (*Table* III). *Gastric acidity:* The stomach was evacuated through a nasogastric tube and the contents were analysed for free and total fasting acid. Histamine phosphate (0.5 ml. of 1:1,000 solution) was injected

TABLE II

SUMMARY OF LABORATORY AND X-RAY DIAGNOSTIC TESTS EMPLOYED

Function Studied	Test Employed	Normal Limits	No. of Patients
Gastric secretion	Uropepsinogen [1]	2,000–4,000 units (24 hr.)	119
	Gastric acid Intubation [2,3]	Fasting: 11–84 units Histamine: 67–90 units	40
	Azure A [4]	0.3–0.6 mg./2 hr.	108
Intestinal absorption	Vitamin A [5]	50 μg. initial value to maximum at 2 hours	37
	Iodine [6]	Iodine-positive saliva in from 6 to 15 minutes	99
	Xylose [7]	4–8 gm. in 5-hour urine	55
Liver function	Bromsulphalein retention [8]	4.9%	455
	Urine urobilinogen [9]	1:32 (1:64)	449
	Icterus index [10]	9.9 units	336
	Bilirubinuria [11]	Negative	449
	Alkaline phosphatase [12]	1.2–3.9 units	404
	Serum bilirubin [13]	0.4–1.19 mg. % total	98
Biliary tract function	Graham Cole series	Filling / Emptying	
	Iodoalphionic acid	3 gm. 3–4+ / 2–4+	24
	Iodoalphionic acid	6 gm. 3–4 / 2–4	24
	Cholographin	15 ml. 3–4 / 2–4	21
Pancreatic function	Serum amylase [14–16]	60–160 units %	209
	Serum lipase [17]	.06–.87 units %	46

subcutaneously and a sample was collected a half hour after injection.

Tubeless technic: Gastric acidity was estimated by the Diagnex® (Azure A) tubeless method.

Results: Intubation (see Table III). Of the forty patients tested twenty-six had little or no total fasting acid. Ten of these had adequate acid following stimulation with histamine, and one patient was unable to tolerate the tube long enough for a determination of his response to histamine. Seven patients had adequate acid both before and after the administration of histamine while six patients had fasting acid values well within the normal range (11 to 42 units) but demonstrated poor response to the administration of histamine. One patient with a normal fasting acid value could not tolerate intubation long enough to evaluate his response to histamine. Gastric analysis was repeated in eleven patients with hypochlorhydria on admission. Of these eight patients remained hypochlorhydric, three had normal values after the administration of histamine on retest. Retests were also obtained in three patients who had normal acid values on admission. In two of them the results were normal on retest, the third had hypochlorhydria.

Azure A Complex. One hundred and eight patients were tested with this resin complex. Of this number thirty-nine had evidence of reduced gastric acid. Six of the patients in this group were retested, four remained hypochlorhydric. Thirty-five patients were tested by both intubation and the tubeless method. The tests were in qualitative agreement in twenty-nine (83 per cent) of the patients, fifteen were hypochlorhydric by both technics and fourteen were normal by both procedures. One patient who had adequate acid on intubation demonstrated little or no acid by the tubeless method, while four patients who seemed hypochlorhydric on intubation had normal values by the tubeless

TABLE III
TEST OF GASTRIC SECRETION

Method	Initial			Retest		
	No. of Patients	Normal	Abnormal	No. of Patients	Normal	Abnormal
Acid						
Intubation:						
Fasting	40	14	26	14	2	12
Posthistamine	38	18	20	14	5	9
Tubeless:						
Azure A	108	69	39	25	18	7

Uropepsinogen							
Initial				Retest			
No. of Patients	Normal	Elevated	Depressed	No. of Patients	Normal	Elevated	Depressed
119	58	45	16	27	6	11	10

method. Thirty-nine per cent of the intubated patients had hypo- or achlorhydria both prior to and following the stimulation with histamine and 36 per cent of the patients tested with azure A demonstrated reduced production of acid.

Several workers [*18–23*] have suggested an association between hypochlorhydria and acute alcoholic gastritis. It is possible that the number of hypochlorhydric patients would have been reduced had samples been obtained two hours after the administration of histamine, as Hirschowitz [*24*] has indicated that maximum response to histamine occurs two hours following stimulation with histamine. However, the technical problems involved in intubating acutely ill, retching alcoholics were such that even the half-hour collections were not always obtained. It is of interest to note that the gastric aspirate was grossly bloody in four patients following the injection of histamine.

Urinary Uropepsinogen (*Table* III). Urine collections made during the twelve hours following admission were tested for uropepsinogen. Of 119 patients tested sixteen had low values, nine were retested and the values remained low on retest. Forty-five patients had high values; only seven patients in this group were retested; of this number three were normal and four had elevated uropepsinogen. Eleven patients with normal tests on admission were rechecked; three remained normal, seven had elevated values and one had a reduced value.

Among the patients tested were ten with previously established gastric abnormalities. (Table I.) Seven had duodenal ulcers, one had a gastric ulcer, two had "hemorrhagic gastritis" and one had hematemesis of unknown etiology. One of the patients with duodenal ulcer and the one patient with gastric ulcers had previously had gastrectomies performed and were found to have depressed uropepsin values; only one of the patients with ulcer had an elevated uropepsin value. An additional patient with hematemesis had an elevated value; however, the cause of bleeding in this case was not determined as the patient left the hospital prior to his scheduled roentgenographic examination. There was no apparent correlation between the gastric disorders and uropepsinogen level in the remaining cases.

Gastric acid (intubation) and uropepsin determinations were performed in the same thirty-five patients. Of these eleven were hypochlorhydric; seven had normal or elevated uropepsinogen values and four had depressed excretion of uropepsinogen. Eleven of the re-

maining thirteen patients had either normal or elevated uropepsinogen in association with normal acid values while two had low uropepsinogen values. The meaning and usefulness of the determination of uropepsinogen as a measure of gastric secretory activity is debated [*1,25–32*]. The significance of the high frequency of elevated uropepsin values observed in our patients remains to be determined, both with respect to their known ulcer diathesis and personality trait.*

Gastrointestinal Absorption (*Table* IV). *Vitamin A tolerance test:* The absorptive capacity of the intestinal tract was tested by determining vitamin A serum levels two, four and six hours after the administration of 5,000 international units per kilogram of body weight of a water-miscible vitamin A preparation† [*33*]. Of the thirty-seven patients studied, three demonstrated marked abnormalities in absorption. Ten of the patients were retested two weeks after admission; in only one of this group was the curve abnormal on admission but normal on retest. Vitamin A was used in aqueous dispersion, as this was thought to be more readily absorbed even in the absence of bile. As the state of the liver and biliary system was not known to be normal on admission, it was thought that the reliability of the test would thus be enhanced.

Iodine absorption test: The ability of the gastrointestinal system to absorb 0.25 gm. of potassium iodide administered orally in 50 ml. of water as determined by testing for the time of appearance of iodine in the saliva. Salivary flow was stimulated by the chewing of gum or paraffin. Of the ninety-one patients tested, sixty-six had a delayed appearance time. Twenty-five of the patients with abnormal results were retested within two weeks, and in eleven results were normal on retest, while fourteen continued to show delayed absorption of orally administered potassium iodide. Rankin [*34*] demonstrated that potassium iodide deposited in the isolated rumen of sheep appeared in the saliva in five minutes, and concluded that iodine was absorbed from the stomach. Cohn [*35*] studied the absorption of iodine from isolated segments of the gastrointestinal tract of intraperitoneally anesthetized dogs. His experiments indicated that 78 to 80 per cent of the iodine placed in the ileum was absorbed. Fullerton and Heath [*6*] applied the iodine absorption test to man, assuming on the basis of the last work cited that it was a test for the absorptive capacity of the ileum.

TABLE IV
TESTS OF GASTROINTESTINAL ABSORPTION

Test	No. of Patients	Normal	Abnormal	Retests on Abnormal Patients		
				No.	Normal	Abnormal
Vitamin A.....	37	34	3	1	1	0
Iodine (KI).....	91	25	66	25	14	11
Xylose.....	55	45	9	1	0	1

Preliminary results of a study [*36*] in this laboratory indicate that in man there is no effective absorption of iodine from the stomach. That is to say, iodine did not appear in the saliva of six normal subjects until there was radiographic evidence that potassium iodide solution (mixed with either barium sulphate or Diodrast®) had passed into the duodenum. Iodine in saliva was detected in from one and a half to two minutes after the solution was allowed to pass from the stomach by altering the position of the subjects.

Since this absorption test is dependent on parotid [*37*] function, the role of this gland was assessed by intravenous administration of potassium iodide to four patients who demonstrated poor absorption with orally administered potassium iodide. Iodine appeared in the saliva two to four minutes after the injection of potassium iodide. It may be assumed, therefore, that dysfunction of the parotid gland was not responsible for the delay. It is possible that the delayed excretion of iodine in alcoholics may have been due to poor gastric emptying, as the normal limits for this test (six to fifteen minutes) are short enough to have been exceeded by a delay in emptying. This hypothesis is weakened, however, by the fact that two patients with abnormal iodine absorption tests had had subtotal gastrectomy.

Xylose tolerance test: The amount of xylose present in a five-hour collection of urine following the ingestion of 25 gm. of xylose has been used as a measure of intestinal absorption. Nine

* These observations appear to confirm the note by Spiro and Schwartz [*72*] who found reduced gastric acid associated with increase in blood pepsin and urine propepsin in cases of superficial gastritis. They attributed this discrepancy between gastric acid and uropepsin measurements to blockage by necrotic cells of the necks of the gastric glands, leading to regurgitation of pepsin into blood.

† Aquasol A.

TABLE IVA
COMPARISON OF RESULTS IN THIRTY-FIVE PATIENTS TESTED WITH BOTH XYLOSE AND IODINE ABSORPTION TECHNICS

No.	Xylose	Iodine
10	Normal	Normal
19	Normal	Abnormal
2	Abnormal	Normal
4	Abnormal	Abnormal

of fifty-five patients tested in this manner demonstrated abnormalities in absorption. One of the patients with abnormal results was retested and the response remained abnormal.

The xylose tolerance test has been employed successfully [*38–42*] in assessment of the absorptive capacity of the intestinal tract in malabsorption syndromes such as sprue (tropical), idiopathic steatorrhea and pernicious anemia. As xylose is not normally found in body fluids and is excreted by the kidney with little or no tubular reabsorption [*43*], it is useful as a test substance for determining the absorptive capacity of the intestinal tract. However, there is continuing controversy as to the mechanism of its absorption. Hele [*44*], Brien [*38*], Davidson [*45*], Farrar [*46*] and Wyngaarden [*47*] have presented evidence which indicates that xylose is absorbed by an active process, while Cori [*48*], Sols [*49*]. Wilson [*50*] and others postulate a simple membrane diffusion phenomenon. In view of the uncertainty of the mechanism involved in absorption, it is impossible to determine the exact metabolic or pathologic significance of the poor absorption observed in many of the alcoholic patients.

One hundred thirty-one patients were tested for malabsorption by one or more of the methods discussed and sixty-six (50 per cent) had abnormal results in at least one of the tests studied. Thirty-five patients were evaluated by both iodine and xylose absorption tests and the results were similar in only fourteen cases. (Table IVA.) As the physiological basis for malabsorption has not yet been elucidated, it is impossible to explain the discrepancy between these two tests.

Such factors as intestinal hypermotility, vitamin deficiency and gastrointestinal inflammation may have played a role in the malabsorption noted in alcoholic patients. Surgical resection of the gut or poor digestion resulting from pancreatic malfunction did not seem to be contributory causes since the two gastrectomized patients tested had normal absorption of xylose, and the pancreatic malfunction encountered was of minor degree and not associated with malabsorption. However, the possible importance of malabsorption in the pathogenesis of hepatic, pancreatic and central nervous system diseases of the chronic alcoholic is worthy of further investigation.

TABLE V
TESTS OF LIVER AND PANCREATIC FUNCTION

Test	No.	Initial Test Normal (%)	Abnormal (%)	Abnormals Retested		
				No.	Normal	Abnormal
Liver Function Tests						
Urine urobilingen	449	335	134	67	63	4
Bromsulphalein	455	432	23	15	12	3
Icto-test®	449	438	11	7	7	0
Icterus index	336	323	13	8	8	0
Serum bilirubin	98	76	22	1	0	1
Alkaline phosphatase	404	354	50	14	11	3
Pancreatic Enzyme Tests						
Amylase	209*	174*	35*	1	0	1
Lipase	46	35	11	..	..	..

* These numbers include tests done by both the rapid and quantitative methods.

Liver Function Tests (*Table* V). *Urine Urobilinogen:* Of 449 patients tested, 134 were found to have elevations of urine urobilinogen on admission. Sixty-four of the patients with abnormalities on admission were retested within two weeks and only four of these continued to have abnormal values.

Normal physiological processes such as eating and heavy muscular exercise may produce elevations in urinary excretion of urobilinogen, as may diseases of the liver, biliary system, infectious diseases, hemolytic disorders and toxic agents. Many of the initial tests were made with the patient in a non-fasting state and it is possible that some minor elevations may have been related to this fact [*51*]. Further, the role of the muscular activity involved in the "shakes" cannot be overlooked.

Of the pathological possibilities listed, some degree of hepatic disease may be postulated on the basis of the frequency of hepatomegaly, also radiographic studies suggest some abnormality in function of the gallbladder or biliary tree. Patients with evidence of infectious diseases were eliminated from the present study and the

routine blood studies obtained gave no evidence of severe hemolytic disorders, so that these factors need not be considered. A great variety of toxic beverages ranging from acetone to zerone were consumed freely by most of the patients studied, and these may have been directly or indirectly responsible for some of the abnormal values obtained. Whatever its cause, the hyperurobilinogenuria was short lived, as most of the patients retested had normal values for urinary excretion of urobilinogen. (Table v.) Binswanger [*52*], Lepehne [*53*] and others [*54–56*] termed the liver abnormality in acutely intoxicated alcoholics "acute transient liver damage." These authors considered the estimation of urine urobilinogen the most sensitive test for assessing this transient disorder. Our data support their findings.

Bromsulphalein retention: Of the 455 patients studied, only twenty-three had values of 5 per cent retention or greater. Twelve of fifteen patients with abnormal results, who were retested after two or more weeks of routine hospital care, were normal on retest, while three continued to be abnormal. Two of the latter three patients were proved to have cirrhosis.

Cates [*54*], Nadeau [*55*], Rouleau [*56*] and others suggested that the bromsulphalein retention test was a most sensitive indicator of the transient liver condition seen in acute alcoholics. However, Seife [*57*] in a histological and functional study of the liver of acute alcoholics found that fifty-six of sixty-five patients had structural abnormalities; forty-seven had some degree of fatty metamorphosis, thirteen had "local fibrosis" (bromsulphalein retention was increased in the patients with fibrosis). Further, Ingelfinger [*58*] showed that bromsulphalein retention may not be altered in patients with fatty liver.

Serum bilirubin: Twenty-two of ninety-eight patients tested had initial serum bilirubin values in excess of 1.2 mg. per cent (range of abnormal values, 1.2 to 3.47 mg. per cent, mean 1.77 mg. per cent). Three of the group with abnormal responses were retested; in one values returned to normal and in the other two, subsequently proved to have cirrhosis, they remained abnormal. The minor elevations in serum bilirubin were probably due to fatty liver and minor disorders of the biliary tract found in many of the alcoholics [*47–59*].

Alkaline phosphatase: Forty-nine of 404 patients tested had minor elevations in serum alkaline phosphatase (between 4.0 to 6.7 units, with only four elevations in excess of 5.0 units). On retest of fourteen patients with elevated values, results in three remained abnormal while eleven had values well within the normal range. Biliary malfunction or fatty liver may have contributed to these minor elevations.

Bilirubinuria: Bilirubin in the urine was detected by the use of a "bilazo" type test (Ictotest®). The urine of nine of 449 patients studied had trace quantities of bile, two had clearly positive tests. Seven of these eleven were retested and the values found to be normal.

Icterus index: Only thirteen of 336 patients had icterus indices in excess of 10. In eight of these values were normal on retest.

The abnormalities in biochemical tests of liver function were almost always of minor degree and promptly returned to normal. Many of the results could be accounted for on a basis of uncomplicated fatty liver. Minor degrees of biliary malfunction may have contributed to the abnormalities. Only two cases of frank cirrhosis were found; in this regard it is unfortunate that liver biopsies were not possible.

Pancreatic Function (*Table* VI). *Serum amylase:* Determinations were made in 209 patients. Of this number 112 were tested by quantitative methods [*14,15*], the remaining ninety-seven by a rapid roughly quantitative iodometric technic [*16*]. Of the 112 quantitatively analysed serums, ninety were normal, twenty-two showed some elevation of serum amylase. Of the ninety-seven patients screened by the rapid iodometric procedure, values were normal in eighty-four, in the questionable range in four, and elevated in nine.

Serum lipase: Serum lipase was determined in forty-six cases; values were elevated in eleven. No retests were made.

The relatively high incidence of pancreatic dysfunction (19.6 per cent amylase, 24.0 per cent lipase abnormalities) is in agreement with the results reported by other workers [*60–62*]. Several authors have suggested mechanisms by which alcohol may produce acute pancreatitis. Egdahl [*63*] expressed the view that pancreatitis may be secondary to an alcohol-induced gastroenteritis. Myers and Keefer [*64*] postulated three mechanisms which, singly or combined, could produce acute pancreatitis in alcoholics: (1) duodenal congestion obstructing the pancreatic ducts; (2) persistent vomiting causing regurgitation into the pancreatic ducts, or (3) direct toxic

TABLE VI
CHOLECYSTOGRAPHY

Medium	Admissions	Normal				Abnormal			
		Initial	Retest			Initial	Retest		
			No.	Normal	Abnormal		No.	Normal	Abnormal
Iodoalphionic acid (6 gm.).....	24	7	7	5	2 {1(F & E) 1(E)	17 {10(F & E) 2(E) 5(F)	13	5	8 {2(F & E), 2(E) 2(F & E), 1(E), 1(F)
Iodoalphionic acid (3 gm.).....	24	6	3	3	0	18 {10(F & E) 3(E) 5(F)	10	8	2 2(F)
Cholographin (15 ml.).....	21	4	2	1	1	17 {11(F & E) 3(E) 3(F)	6	2	4 2(F & E), 2(F)

NOTE: (F) = Filling deficit. (E) = Abnormal emptying.
Films were taken using the same radiologic factors on admission and retest to permit comparison. The degree of filling was established as follows: 4 plus equalled the radiopacity comparable to that of the bony structures of the spine, 1 plus was the minimal amount of radiopacity permitting identification and localization of the gallbladder, 2 and 3 plus were intermediate degrees between these extremes. Emptying was interpreted on the following basis: 4 plus indicated total disappearance of the gallbladder image forty-five minutes after ingestion of a fatty meal (containing 1 egg yolk 3 ounces of milk, 3 ounces of cream and 2 pats of butter) while 1 plus denotes an increase in opacity without appreciable change in the size of the gallbladder. Two plus was considered the lowest limit of normal response and indicated the reduction of the gallbladder shadow to one-half of its filled size.

effect of elevated blood alcohol on the pancreas. Rich and Duff [*61*], observing that many attacks of acute pancreatitis occurred following the ingestion of a heavy meal or large quantities of alcohol, inferred that pancreatic secretory volume was related to the size of the ingesta and that the excessive pancreatic pressure applied against abnormal resistance in the ductal system caused pancreatitis. On postmortem examination they found that thirteen of twenty-four patients who had died with acute pancreatitis had ductal metaplasia of the pancreas. They concluded that this metaplasia might have been the cause of the abnormal resistance which they postulated. Dreiling [*65*] postulated that alcohol produced excessive pancreatic flow via the secretin mechanism and attributed the obstruction to spasm and edema of the papilla; the sudden increase in intraductal pressure causing rupture of the fine radicals of the pancreatic tree. The possible role of nutritional deficiency in the etiology of pancreatitis in the alcoholic patient remains to be studied.

Biliary Tree and Gallbladder (*Table* VI). *Cholecystography and intravenous cholangiography:* A total of sixty-nine patients were studied. A double oral dose of iodoalphionic acid (6 gm.) was used in twenty-four patients studied. Twenty-four patients were studied with a single dose (3 gm.) of the same preparation, and an intravenous preparation (Cholografin®) was used in twenty-one patients in order to assess the factor of intestinal absorption.

No significant differences were observed in the results obtained by the three methods employed. Of the sixty-nine patients tested, thirty-one had deficits in both filling and emptying of the gallbladder, thirteen had incomplete filling alone and eight had poor emptying. Twenty-nine of the fifty-two patients with abnormalities were retested within two weeks following admission. Nineteen of these patients showed improvement, three were worse and seven were essentially unchanged.

Although there was no evidence of cholelithiasis, the number of non-visualized and/or radiologically functionally subnormal gallbladders was high (75 per cent) in the present study. On retest fifteen of the twenty-nine patients with abnormal findings had normal findings.

The factors which may have been responsible for the largely reversible abnormalities noted include the following [*66*]: (1) failure of absorption of the medium resulting from diarrhea, pancreatic disease, or abnormality of the small intestine; (2) impairment of hepatic function with reduced excretion of the dye; (3) precocious emptying of the gallbladder; and (4) physiological stasis.

Although malabsorption might have contributed to some of the deficits noted, it clearly was not the sole cause since approximately the

same number of abnormalities were noted in patients studied by intravenous cholangiography.

It is unlikely that impaired hepatic function caused the apparent biliary dysfunction since Etess and Strauss [*67*] have shown that oral cholecystography was satisfactory in patients with abnormal responses to liver function tests far in excess of any seen in the present series. As the majority of alcoholics studied had not eaten adequate meals for many days prior to admission, it is possible that the "physiological stasis" postulated by Brewer [*68*] contributed to the observed filling and emptying deficits. In Brewer's study [*68*] it was noted that patients taking inadequate, fat-free diets demonstrated radiologically deficient gallbladder function which returned to normal following a period of adequate feeding. Brewer attributed the poor filling to incomplete replacement of the thick inspissated gallbladder contents with fresh, dye-laden bile.

COMMENTS

The present study was undertaken in an attempt to assess the functional significance of the digestive tract symptoms of the skid row alcoholic usually loosely diagnosed as "alcoholic gastritis." Abnormalities were revealed in each digestive organ studied. There was a high frequency of minor impairments of liver function, minimal but consistent deficits of gallbladder and pancreatic function, and a relatively high frequency of abnormal responses to tests of intestinal absorption. Many of these abnormalities were promptly reversible. A high percentage of patients showed evidence of reduction in gastric acid by direct or indirect testing. The relative infrequency of severe abnormalities in liver function was surprising.

These functional changes may represent early stages of the more serious disorders of these organs such as cirrhosis, acute pancreatitis and hemorrhagic gastritis. Alcohol and dietary imbalance are commonly considered to be somehow related to these conditions and much has been published with regard to the disorders of the liver and pancreas.

Gastritis has been produced experimentally with alcohol [*23*] but relatively little is known concerning the possible relationship between intestinal malabsorption and the drinking episode [*24*]. It is of interest, however, that rats receiving alcohol [*71*] also show a diminished xylose absorption.

Dietary imbalance alone [*69,70*], and alcohol alone [*22*], have deranged the normal metabolism of, and frequently produced pathologic lesions in the gastrointestinal mucosa of the rat. It is likely that the deficient diet of the chronic alcoholic coupled with the toxic insult of alcohol produces metabolic changes in this highly susceptible tissue. Such changes as these along with the demonstrated hypochlorhydria, which has been shown to impair the absorption of B vitamins, may in part be responsible for the malabsorption observed. Further, it is quite possible that a combination of pathologic changes and malabsorption may contribute to the dysfunction of the other organs of the digestive system.

SUMMARY

A study of the digestive system of skid-row alcoholics at the termination of a drinking episode revealed varying degrees of physiologic disturbance of one or more of the digestive organs. These functional alterations were usually minor and were frequently transient. The disturbances noted were: (1) reductions in gastric hydrochloric acid; (2) variations in urine uropepsin values above and below normal; (3) increases in serum lipase and amylase suggestive of subacute pancreatitis; (4) hepatomegaly accompanied by minor and transient alterations of liver function tests; (5) transient minimal deficits of gallbladder filling and emptying, and (6) frequent abnormalities in the tests for intestinal absorption of xylose and potassium iodide.

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The Syndrome of Congenital Goiter with Butanol-Insoluble Serum Iodine*

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SEVERAL reports [*1–3*] have recently appeared in which are described patients with congenital goiter and hypothyroidism who have an abnormal iodinated substance in the blood. The substance is recognized by its failure to extract into n-butanol from the acidified serum. In these patients thyroxine and triiodothyronine are not synthesized in adequate amounts. Marked physical and mental retardation may result unless the condition is recognized and treated within the first years of life.

In the present report five additional cases of this syndrome are described. The results of studies on the iodinated components of the serum and urine, and of the distribution of RaI^{131} and protein in the thyroid glands in two of these cases will be presented.

METHODS‡

Methods of measurement of thyroidal radioactive iodide uptake, retention and release, extraction of serum and urine, chromatography, enzymatic digestion [*2*] and starch block electrophoresis of serum are described elsewhere [*4*]. Protein-bound $iodide^{131}$ was measured by precipitating 1 to 2 ml. of serum with four volumes of 20 per cent trichloracetic acid (TCA) and washing the resuspended precipitate twice with 5 per cent TCA. Butanol solubility of I^{131}-labeled components was determined by acidification of the sample to pH 2 with 1 N H_2SO_4, and subsequently extracting once with 4 to 5 volumes of n-butanol saturated with 5 per cent sodium thiosulfate and twice with n-butanol saturated with water. More than 90 per cent of labeled iodine present in the serum of normal subjects after administration of RaI^{131} is extracted by this process.

Thyroid glands obtained at operation were transported to the laboratory in cracked ice. Representative portions, excluding hemorrhagic areas, were weighed, minced and homogenized in chilled isotonic saline solution with a ratio of tissue: saline of 1:4, and filtered through cheesecloth. Portions of homogenate were used for determination of *in vitro* deiodination activity [*5*]. The homogenate was then fractionated by sedimentation in a refrigerated centrifuge at 600 times gravity (× g), 10,000 × g, and 100,000 × g. The sedimented particulate fractions and final supernatant were collected and diluted to appropriate volume in isotonic saline solution.

Aliquots of all particulate fractions and final supernatant were examined by paper electrophoresis in pH 8.6 barbital buffer at ionic strength 0.1, 70 volts, 5 ma. for eight to fourteen hours, and subsequently stained with amidoschwarz in methanol-glacial acetic acid. The 100,000 × g supernatant was digested with chymotrypsin [*2*] and examined by chromatography in butanol-water-glacial acetic acid (8.5:7.5:1) or butanol-isoamyl-ammonia (1:1:2) solvent systems. The 100,000 × g supernatant (thyroid saline extract) was diluted to 0.5 per cent protein concentration with isotonic sodium chloride and examined in the Spinco Model E Analytical Ultracentrifuge.§ When necessary, further observations were made with a partition cell. The material above and below the dia-

‡ The following abbreviations will be used in this report: MIT-monoiodotyrosine, DIT-diiodotyrosine, T_3-triiodothyronine, T_4-thyroxine, PBI-protein-bound $iodide^{127}$, TBP-thyroxine-binding protein, PBI^{131}-protein-bound $iodide^{131}$, $NBEI^{131}$-non-butanol extractable I^{131}.

§ We are indebted to Dr. Karl B. Schmid for his cooperation in these studies.

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phragm was separately collected for electrophoresis or other studies.

Salting out of thyroglobulin was accomplished by a variation of the technic described by Robbins [*6*] with 0.1 to 0.2 ml. of thyroid saline extract in 2 ml. of solution of pH 6.75 phosphate buffer ranging from .8 to 2.34 M. After ether flocculation [*8*] of insoluble proteins, aliquots were taken for determination of soluble protein [*7*] and radioactivity.

Labeled iodine was measured in serial sections of paper strips or aliquots of liquid samples in a well-type scintillation gamma-ray detector.

Thyroid protein fractions were prepared in a Model CP Spinco Paper Curtain Electrophoresis apparatus. Samples containing about 600 mg. protein were run for twelve hours in pH 8.6 barbital-barbiturate buffer, ionic strength 0.02, at 55 ampers, 800 volts, and 4°C. Fractions of 10 to 20 ml. were collected from the bottom of the curtain, concentrated by dialysis against 50 per cent polyvinyl pyrrolidone in isotonic saline solution, and diluted to an appropriate volume (1 to 2 ml.) in isotonic sodium chloride solution.

CASE REPORTS

CASE I. (MGH No. 429695). The patient (E. J.) was a twenty-eight year old woman. Chronologically the first case observed, a detailed report on this patient has recently appeared [*2*]. This congenitally goitrous and cretinous woman was studied for thirteen years following subtotal thyroidectomy for goiter. There was rapid uptake and release of I^{131}. Potassium thiocyanate induced no release of iodide from the gland. Thyroxine and non-butanol extractable iodide^{131} were found in her serum. The abnormal I^{131}-labeled protein moved with albumin on starch block electrophoresis, was non-dialyzable, and liberated MIT, DIT, T_3 and T_4 on enzymatic hydrolysis. Normal levels of TBP were present. *In vivo* DIT deiodinated was normal. Iodide and a non-butanol soluble iodinated component were found in the urine.

CASE II. (MGH No. 928074). This ten year old girl (R. A. M.) was considered normal at birth. She walked at thirteen months but did not learn to talk until she was thirty-six months old. She was mentally dull, easily fatigued, irritable, obese, constipated, and had a lump in her neck. Hypothyroidism was diagnosed at the age of eight. Replacement therapy produced improvement in the symptoms of hypometabolism but no significant change in mental function. The goiter decreased in size. There was no similar disorder in the family. The patient was admitted to the hospital for study two months after desiccated thyroid therapy was discontinued. During this interval the hypometabolism reappeared, and the goiter became larger.

The patient was an obese (24.5 kg.), shy, dull child who was short (115 cm.) for her age. The blood pressure was 95/70 mm. Hg and pulse 72. The skin was warm, dry and coarse. The thyroid was three to four times enlarged, smooth, of normal consistency, and without bruit or thrill. *In vivo* DIT deiodination was normal. The uptake of I^{131} was 66 per cent in two hours and 71 per cent at twenty-four hours. There was a rapid turnover of iodine by the gland ($T\ ½ = 12$ days. No I^{131} was released from the gland after the administration of potassium thiocyanate. PBI^{131} was .39 per cent/L., and the conversion ratio was 67 per cent at forty-eight hours. Half of the serum protein-bound RaI^{131} was insoluble in butanol. Sixty-three per cent of PBI^{131} traveled with albumin on starch block electrophoresis. Butanol solubility of serum I^{131} (control = 65 per cent was increased following enzymatic digestion of plasma to 91 per cent.

Butanol extracts of serum chromatographed in the butanol-acetic acid or butanol-isoamyl-ammonia systems revealed iodide and thyroxine. The presence of small quantities of MIT and DIT was suggested. Butanol extracts of urine demonstrated small amounts of MIT, DIT and iodothyronine (T_4 and/or T_3) on chromatography.

Twenty per cent of the labeled iodine of the urine was insoluble in butanol. This material was not further characterized. Thyroid tissue was not available for study.

CASE III. (MGH 184120). The patient (P. F.) was a forty-two year old man. His birth and infancy were normal. There was no retardation of physical growth. He did poorly in school and completed his education in a trade school. A goiter was found at the age of fourteen, but there were no symptoms of hypometabolism. Because of symptoms of compression which developed as the goiter gradually enlarged, subtotal thyroidectomy was performed at the age of twenty-three. Histologic examination disclosed hyperplasia and involution. Postoperatively there were no symptoms of hypometabolism, and thyroid hormone replacement therapy was not given. The basal metabolic rate was −2 to −7. At age thirty-seven a goiter was again found but was asymptomatic despite gradual growth. Because of difficulties experienced in passing a pre-employment physical examination, the patient entered the hospital for evaluation and therapy. The patient's mother, deceased, had had a goiter. One sister died at the age of thirteen following an operation for the removal of a goiter. One brother and one sister are presumed well, although not available, so far, for examination.

The blood pressure was 120/70 mm. Hg and pulse 72. The patient was well developed and nourished. His skin, tongue and reflexes were normal. The thyroid was four times its normal size, lobulated, and

TABLE I

DISTRIBUTION OF RaI^{131} IN FRACTIONATED THYROID HOMOGENATE (CASE II)

Fraction	Per cent of Total I^{131}	Butanol Soluble I^{131} (%)	Preparation of Sample	Distribution of I^{131} on Chromatography (%)				
				I	MIT	DIT	T_3-T_4	Origin Area
600 × g. sediment (nuclei and debris)	0.3	..	Chymotrypsin digestion	21	21	11	4	31*
10,000 × g. sediment (mitochondria and microsomes)	0.008	..	Chymotrypsin digestion	19	17	3.2	15	34*
100,000 × g. sediment (microsomes)	0.05	..	Chymotrypsin digestion	12	16	7	4	52*
100,000 × g. supernatant (thyroid saline extract)	99.6	..	Chymotrypsin digestion	9	21	40	3.2	21*
100,000 × g. supernatant (thyroid saline extract)	.....	11	Butanol extraction	6	26	14	4.7	30

* These samples were not completely digested in fourteen hours.

without bruit or thrill. He stammered, and his intelligence was less than average.

Thyroid studies were performed after the administration of 500 μc. of I^{131}. The thyroid uptake of labeled iodine was 60 per cent at two hours and 82 per cent at twenty-four hours. The turnover was normal ($T\ ½ = 145$ days). At forty-eight hours the total serum I^{131} was 0.05 per cent/L., PBI^{131} 0.032 per cent/L., and $NBEI^{131}$ was 0.012 per cent/L. $NBEI^{131}$ was thus 24 per cent of total I^{131}, or 39 per cent of PBI^{131}. Chromatograms of butanol extracts of serum revealed only iodide and iodothyronine (T_3 and/or T_4). Digestion of serum with chymotrypsin increased the extractability of I^{131} from 69 per cent to 91 per cent.

Chromatography of urine directly or after butanol extraction revealed almost all the radioactivity in the iodide zone. Less than 3 per cent of urinary iodide was $NBEI^{131}$.

Thyroid tissue was obtained at the time of subtotal thyroidectomy. *In vitro* deiodination of MIT was normal. After centrifugal fractionation of the homogenate, 99 per cent of the labeled iodine was found in the 100,000 × g supernatant. Distribution of I^{131} among the chromatographically separated iodoamino acids after digestion of 100,000 × g supernatant showed 21 per cent as MIT, 25 per cent DIT and 3 per cent as $T_{3\ to\ 4}$. The percentage distribution of I^{131} after chromatography of digests of the three particulate fractions appears in Table I. Eleven per cent of the labeled iodine in the 100,000 × g supernatant was butanol soluble. On chromatography this moved as MIT (26 per cent), DIT (14 per cent) and $T_{3\ to\ 4}$ (4.7 per cent).

A non-iodinated protein with the electrophoretic, ultracentrifugal, and immunologic properties of serum albumin was found in high concentration in the thyroid saline extract. Present on paper electrophoresis of the 100,000 × g supernatant were the thyroglobulin band, and a diffuse area of protein

TABLE II

PERCENTAGE DISTRIBUTION OF PROTEINS AFTER ULTRACENTRIFUGATION

Component	I	II	V
Case III (patient P. F.)	None	$S^{\circ}_{w,20}$ = 19.4 51 per cent	$S^{\circ}_{w,20}$ = 4.26 49 per cent
Normal control human thyroid	$S^{\circ}_{w,20}$ = 29 6 per cent	$S^{\circ}_{w,20}$ = 19.6 77 per cent	$S^{\circ}_{w,20}$ = 4.27 17 per cent

TABLE III

PER CENT DISTRIBUTION OF I^{131} IN CHROMATOGRAMS OF SERUM BUTANOL EXTRACTS AND URINE (CASE IV, PATIENT C. C.)

Time after Administration of I^{131} (hr.)	Sample	Percentage Distribution of I^{131}			
		I	MIT	DIT	T_3–T_4
1	Serum	82	.....	....	.....
8	Serum	26	15	13	24
24	Serum	9	10	9	39
48	Serum	12	14		45
24–48	Urine	45–52	3	4–6	4–01

staining occupying a position analogous to plasma beta-gamma globulins. In addition, a large portion of the protein was observed ahead of thyroglobulin in the position of serum albumin. (Fig. 1.) This band contained no I^{131} by radioautography. Preparative electrophoresis on a paper curtain did not resolve the prethyroglobulin component, but the protein-containing area was found to extend anodaly ahead of the I^{131}-containing area. Ultracentrifuge analysis of proteins in the leading and trailing edges of the I^{131}-containing peak from the curtain electrophoresis revealed the presence of $S^{\circ}_{w,20} = 4$ material in both areas, relatively enriched in the leading edge.

Ultracentrifugation of a 0.5 per cent protein preparation of the 100,000 × g supernatant in isotonic saline solution demonstrated two major components with a distribution quite different from normal. (Fig. 2, Table II.) The components are designated in accordance with the scheme used by Shulman [*14*] in ultracentrifuge analysis of pig thyroid saline extracts. Component II is thyroglobulin. Components I and V are not fully characterized. The smaller components (III, IV) noted by Shulman were not detected in these studies. Apparently the prethyroglobulin protein sedimented with the normal $S^{\circ}_{w20,} = 4$ proteins, although no hint of two peaks appeared in the pattern. Sedimentation of the $S^{\circ}_{w,20} = 19$ protein beyond the diaphragm in a partition cell carried over 90 per cent of the I^{131} with it.

I^{131}-labeled protein in the thyroid saline extract was salted out of solution by 2 to 2.3 M phosphate buffer.

There appeared to be complete immunologic identity of the prethyroglobulin "thyroid" protein with serum albumin. Ouchterlony plates were employed, using rabbit antihuman serum albumin or horse antihuman serum for antibody in the center well, and dilutions of human serum albumin or thyroid saline extract as antigen in the circumferential wells. Precipitation occurred central to each well within twenty-four hours, and a line of identity with human serum albumin was found. There were other weak zones of precipitation central to the well containing the strongest concentration of thyroid extract. When horse antihuman serum was the antibody, these weak zones were closely related to zones of precipitation formed against patient's serum. When thyroid extract was incubated at 20 degrees for ten hours with an excess of rabbit antihuman serum albumin, the prethyroglobulin spot was no longer demonstrable in the electrophoretograms.

CASE IV. (MGH No. 1016033). This patient (C. C.) was a fourteen year old girl who developed slowly during infancy. Goiter was first observed at the age of four. With desiccated thyroid therapy further intellectual and physical growth were normal, and the goiter disappeared. One year prior to admission the administration of 1½ gr. desiccated thyroid daily

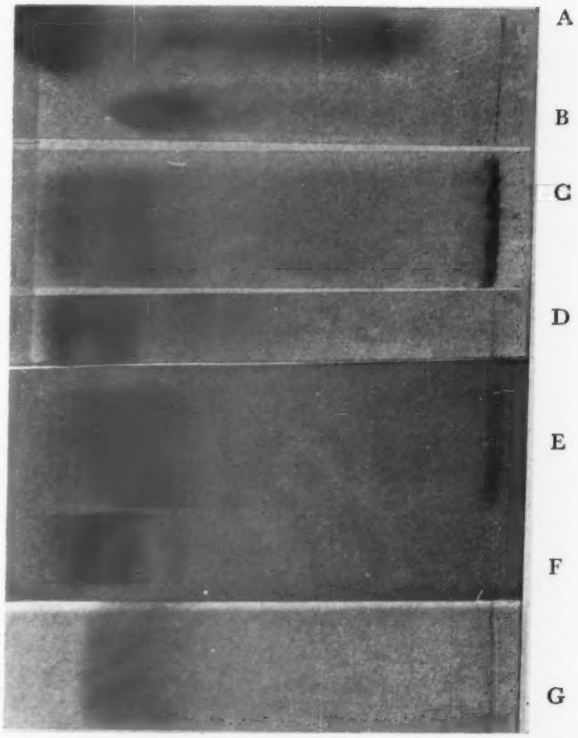
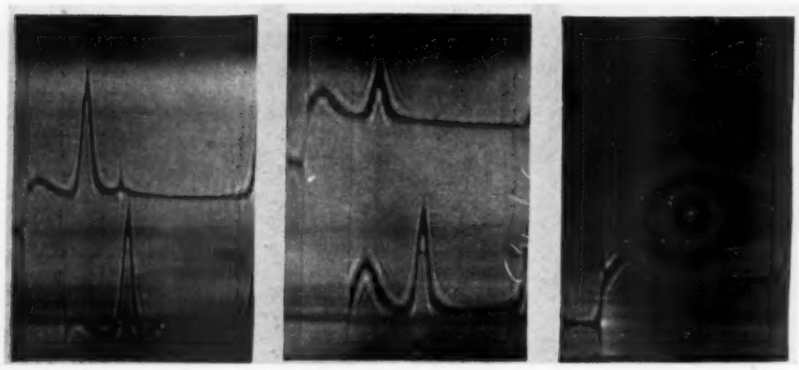


FIG. 1. Electrophoretograms of serum, thyroglobulin and thyroid extracts. Direction of migration is to left. A, normal serum. B, purified pig thyroglobulin. C, thyroid homogenate (Case III). D, thyroid saline extract (Case III). E, radioautograph of C. F, radioautograph of D. G, normal human thyroid saline extract. Note position of pig thyroglobulin slightly ahead of serum α_2 globulin, and the corresponding location of the thyroglobulin band in other preparations. The prethyroglobulin band in C and D contains little or no RaI^{131}.

was discontinued. The patient noted some fatigability and heavy menstruation, but no other symptoms that could be attributed to hypometabolism. The goiter reappeared and grew during the year. There was no familial history of thyroid disease.

The patient was a large, intelligent young girl. There was perifollicular hyperkeratosis of the arms and thighs. The skin was dry. The thyroid was enlarged four times its normal size, was firm, and had a bruit and thrill. Physical examination was otherwise within normal limits. The hemoglobin was 11 gm. per cent, cholesterol 156 mg. per cent and PBI 3 μg.

After oral administration of 400 μc. I^{131} the thyroid uptake was 50 per cent at one hour and 85 per cent at twenty-four hours. The half time of thyroidal I^{131} retention was 8.3 days. At forty-eight hours total serum I^{131} was 0.44 per cent/L., PBI^{131} was 0.19 per cent/L., and conversion ratio was 44 per cent. Thirty-three per cent of serum PBI^{131} at forty-eight hours was $NBEI^{131}$. This component built up early (74 per cent of PBI^{131} at eight hours) and then fell to 33 per cent at forty-eight hours, and 19 per cent at five days. The serum after eight hours contained thyroxine,



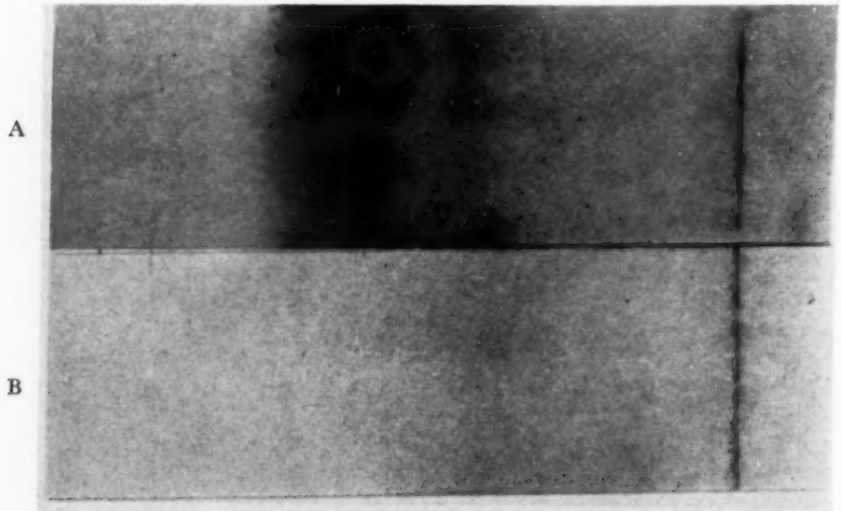
A B C

FIG. 2. Ultracentrifuge patterns of thyroid extracts in isotonic saline solution. A, upper normal thyroid, 0.5 per cent protein; lower: normal thyroid, 0.5 per cent protein. B, upper: Case III, 0.25 per cent protein; lower: same case, 0.5 per cent protein. C, Case IV, 0.5 per cent protein. Direction of migration is to the right. Time of sedimentation, fifty-five minutes. The first small peak (I) in A is $S^{\circ}_{w,20} = 29$. The major peak (II) is thyroglobulin with $S^{\circ}_{w,20} = 19$. The last peak is $S^{\circ}_{w,20} = 4$. Note large proportion of $S^{\circ}_{w,20} = 4$ material in B and absence of thyroglobulin peak in C.

iodide, and possibly small quantities of MIT and DIT. (Table III.) Chymotrypsin digestion of plasma samples increased the extractability of labeled iodine from 77–81 per cent to 93–95 per cent.

Radioactivity in the initial urine samples was present almost entirely as iodide. After eight hours, butanol extracts of urine contained minimal quantities of labeled iodine which chromatographed in the location of MIT, DIT, and iodothyronine carrier. Fifteen per cent of urine I^{131} was $NBEI^{131}$. This material was dialyzable through cellophane tubing. The butanol solubility of the abnormal urine constituent was not affected by incubation with glucuronidase or chymotrypsin but was increased after incubating with 0.1 N H_2SO_4 for twelve hours or boiling with 6 N HCl for one hour. This component moved a few centimeters away from the origin in the acid chromatograph solvent system but remained close to the origin in the alkaline system.

Thyroid tissue obtained by biopsy was prepared in the usual manner. The homogenate deiodinated MIT. Electrophoresis of the 100,000 × g supernatant (thyroid saline extract) revealed a weak protein band in the prethyroglobulin zone and the usual proteins with a mobility analogous to plasma beta-gamma globulin, but no thyroglobulin. (Fig. 3.) Upon radio-



A

B

FIG. 3. Electrophoretograms of thyroid saline extracts. The direction of migration is to the left. A, normal human thyroid. B, Case III. The prethyroglobulin component is barely visible. No thyroglobulin band is present in this electrophoretogram.

TABLE IV

PER CENT DISTRIBUTION OF I^{131} IN THYROID SUB-CELLULAR FRACTIONS, AND IN CHROMATOGRAMS OF DIGESTS OF THESE FRACTIONS (CASE IV, PATIENT C. C.)

Fraction	Per cent of Total I^{131}	Origin	I^-	MIT	DIT	T_3-T_4	Solvent Front
600 × g. sediment (nuclei and debris)	15	32*	20	24	11	11	3.6
10,000 × g. sediment (mitochondria and microsomes)	8	34*	19	21	10	9	1.9
100,000 × g. sediment (microsomes)	5	39*	20	14	8	9	4
100,000 × g. supernatant (thyroid saline extract)	72	37*	24	14	10	7	4

* These samples were not completely digested in fourteen hours.

autography some of the I^{131} was found in the prethyroglobulin area, but most was in the "β-γ" area. In Ouchterlony plates a precipitate formed against rabbit antihuman albumin. Thyroid saline extract was incubated at 20 degrees for twelve hours with an excess of antibody, and the precipitate was separated by centrifugation. The weak prethyroglobulin protein band was still visible in electrophoretograms of the supernatant. The ultracentrifuge pattern consisted of one peak with $S^{\circ}_{w,20} = 4$. (Fig. 2.) Thyroid saline extract protein and I^{131} were gradually salted out of solution with addition of phosphate buffer between 2 and 2.5 molarity. Aliquots of the cellular fractions derived from centrifugation were assayed for I^{131} content and digested by chymotrypsin. Table IV indicates the considerable quantity of radioactivity found with the particulate fractions and the per cent distribution of I^{131} in these fractions.

CASE V. A fifteen year old boy (G. H.) who is a patient of Dr. B. Courvoisier (Geneva), will be reported on in full elsewhere. Myxedema and goiter were present during the first few years of life. His PBI^{127} was 5.2 gamma per cent, and RaI^{131} uptake at twenty-four hours was 90 per cent. After administration of I^{131}, samples of frozen serum and urine were shipped by air to Boston for special studies. The serum at seventy-two hours contained 0.69 per cent of the dose/L. Sixty per cent of the PBI^{131} was not extractable into butanol. Thyroxine, triiodothyronine, iodide and possibly MIT and DIT were identified in the serum. Chymotrypsin digestion increased the butanol solubility of serum $iodide^{131}$. The butanol-insoluble component traveled with albumin on paper curtain electrophoresis of serum. It did not salt out of solution with phosphate buffer of less than 2.2 M. Twenty per cent of the RaI^{131} in the urine was insoluble in butanol. Substances exhibiting the R_f of iodide, MIT and DIT, and an unidentified I^{131}-labeled compound with R_f lower than iodide in the acid solvent system were demonstrated in the urine. The thyroid tissue has not been studied.

CASE VI. This seventeen year old boy (M. H.) is the brother of the patient described in Case V. He is a patient of Dr. B. Courvoisier, and will also be fully reported on elsewhere. This patient had myxedema and goiter during the first few years of life. His PBI^{127} was 1.5 μg. per cent and RaI^{131} uptake 84 per cent. At ninety-six hours the serum contained 0.1 per cent dose/L. total I^{131}, 0.05 per cent/L. PBI^{131} and 35 per cent of PBI^{131} was $NBEI^{131}$. On chromatograms of serum butanol extracts, only iodide was definitely identified. The presence of T_3 and/or T_4 was suggested, but not proved, because the samples were of low activity. During the first twenty-four hours only $iodide^{131}$ was identified in the urine. The urine sample collected from 72 to 96 hours contained 15 per cent $NBEI^{131}$. Chromatograms demonstrated $iodide^{131}$, and possibly MIT and DIT. In addition, a component with R_f less than iodide in the acid solvent system and immobile in the alkaline system was identified. This component was not further characterized.

COMMENTS

Sporadic congenital cretinism with goiter has been frequently described during the last half century [*24–26*]. Recently four distinct groups from this population have been categorized on the basis of specific defects in the process of thyroid hormone synthesis. The first group reported lacks the ability to oxidize iodide and form iodotyrosines, although the thyroid is able to concentrate iodide effectively [*15*]. Patients in the second group synthesize thyroid hormone but cannot deiodinate the MIT and DIT which is normally formed in the hormonogenic process. These amino acids together with their iodine are lost from the gland and excreted in the urine, thereby inducing an endogenous iodine deficiency [*16*]. The third variety, which presumably lacks the ability to couple iodotyrosines into iodothyronines, has been reported

but direct observation of the synthetic defect is not yet available [*17,18*]. The fourth group, the subject of this report, is distinguished by an abnormal iodinated polypeptide or protein in the serum. This substance is recognized by its incomplete extraction from acidified serum into n-butanol.

These syndromes have recently been reviewed in several publications [*3,19,20*]. From observations already at hand, it seems probable that each category represents a specific enzymatic defect. It seems highly probable that other groups are yet to be defined.

In addition to the six cases forming this report, four cases almost certainly fitting the syndrome have been reported by others. DiGeorge and Pashkis described [*1*] a seven and a half year old hypothyroid girl with a goiter, who had 51 per cent butanol insoluble serum I^{131}, RaI uptake of 64 per cent at twenty-four hours, and PBI of 7.7 μg. Similar findings were observed in a twelve month old child. Stanbury and McGirr [*3*] studied two hypothyroid sisters with goiters in whom 40 to 50 per cent of serum I^{131} was not butanol extractable. The first case in the present series was previously reported [*2*].

Several other reported cases may be representative of the syndrome. In an abstract Whitelaw, Thomas and Reilly described a cretin without a goiter who had high levels of serum PBI and increased thyroidal I^{131} uptake [*21*]. Clayton and Smith [*22*] reported six euthyroid siblings, four with goiter, of whom two had PBI^{131} levels higher than BEI^{131}. Thyroidal I^{131} was released in part after the administration of potassium thiocyanate. Studies on the non-butanol extractable iodide were not reported. Werner, Block and Mandl [*23*] described an adult without a goiter who had symptoms and signs of hypopituitarism, normal PBI^{127}, normal RaI^{131} uptake, but with 32 per cent of serum I^{131} present as "iodoprotein." These cases cannot be definitely identified with the group under study, since data in each case are at considerable variance with our own experience up to the present time.

All our patients have had goiters, and five of the six patients described in this study had goiter within the first few years of life and were definitely hypothyroid. Three of the six have a familial incidence of thyroid disease. Each patient had an elevated thyroidal RaI^{131} uptake, and all had normal or low PBI at the time studied. All released a significant quantity of butanol insoluble I^{131} into the serum. Butanol solubility of the abnormal serum component was increased by chymotrypsin digestion, and in one case it was possible to detect iodotyrosines and iodothyronines released by this digestion. When tested, deiodinase activity and serum thyroxine-binding protein have been normal. Potassium thiocyanate has not released I^{131} from their thyroids.

In these subjects the hypothyroidism responded to standard dosage of desiccated thyroid. In each instance, hormone replacement therapy prevented further growth of the goiter or caused marked reduction in its size. Biopsy specimens of thyroid tissue in two instances demonstrated extreme hyperplasia, and in the third, hyperplasia and involution. In no instance has malignancy developed.

The findings in Case III (patient P. F.) are somewhat atypical in that goiter was not noted until the patient was twelve years old, and the gland showed hyperplasia and involution on pathologic examination when the patient was twenty-three. However we believe that the early age of onset in this man, who had evident mental retardation, a strong familial history of thyroid disease, and chemical findings in common with the other patients, warrants his inclusion in this group. The pathologic picture of hyperplasia and involution may have been the result of unusually long-standing hyperplastic stimulus.

In five cases a significant proportion of urinary iodide was present as an unidentified butanol insoluble component, probably a polypeptide, since it was dialyzable in the patients tested.

Examination of thyroid tissue specimens from two patients provided evidence of marked deviation from the normal composition but no explanation for the synthetic defect. The tissue in patient P. F. (Case III) had a low [*12*] portion of I^{131} in the particulate elements; 99.6 per cent of the I^{131} was in the thyroglobulin. Ultracentrifugal analysis demonstrated an increase in the proportion of $S^{\circ}_{w,20} = 4$ material. This was explained by the presence of a large quantity of a protein migrating electrophoretically in the albumin area and precipitable by antihuman serum albumin.

The evidence at hand suggests that this protein was identical to serum albumin, although (1) it was present in remarkably high concentration (roughly 5 gm. per cent) and (2) other serum proteins were not detected in significant amounts

in the tissue. A normal thyroidal protein, "thyralbumin" [*13*], which has the same physical characteristics as albumin but is different immunologically, has been reported but is of unknown relationship to the protein present in our patients. The presence of albumin in the gland may have been related to the necrosis and hemorrhage visible in the tissue, although every effort was made to secure healthy, non-bloody portions of tissue for analysis. Salting out of thyroglobulin (Case III) occurred at 2 to 2.3 M phosphate buffer and thus suggested increased solubility of the iodinated molecule, since normal thyroglobulin is insoluble in 1.75 M phosphate buffer [*6*]. No component was detected corresponding to a hypothetical thyroidal precursor of the serum iodoprotein.

The complete absence of detectable amounts of thyroglobulin in the thyroid of patient C. C. (Case IV) was surprising but was confirmed by the histologic picture of extreme hyperplasia and the virtual absence of colloid. The gland contained a small quantity of prethyroglobulin protein which was weakly labeled with I^{131}. Although the tissue extract contained a protein which precipitated with rabbit antihuman serum albumin, the prethyroglobulin protein band was not removed from the electrophoretogram by this antibody. A large fraction of thyroidal I^{131} was associated with the cell particulate fractions. A similar abnormality in distribution of RaI^{131} among the particulate fractions of thyroid tumor cells has been reported [*9*], but is of unknown significance. The "prethyroglobulin" found in the tissue extract may have been the source of the abnormal serum iodinated compound, but this hypothesis has not been proved.

A tentative formulation of the pathogenesis of this syndrome can be offered. These patients apparently suffer from common or closely related congenital disorders of variable severity. If the defect is marked, the patient has infantile hypothyroidism and retarded development. Goiter develops early and is persistent unless the need for thyroid hormone is satisfied exogenously. The gland forms and secretes a metabolically inactive iodinated protein or polypeptide, in addition to thyroxine. Serum thyroxine and triiodothyronine, and perhaps MIT and DIT, may also be derived from the peripheral metabolism of the abnormal iodinated peptide-linked complex. The secretion of iodoprotein is a shunt of normal hormonal precursors into a useless pathway. The pituitary responds to induce thyroid hypertrophy, which may be adequate to compensate for the defect (Case III), but in severe dysfunction (Cases I and II) is not adequate.

The abnormal circulating complex contains peptide-linked iodotyrosine and iodothyronine. It moves electrophoretically with albumin, is butanol insoluble, and immobile chromatographically. Its molecular weight has not been established. Because it contains iodinated amino acids, it presumably is related to thyroglobulin. Its metabolic fate may be hydrolysis in some body tissue or possibly excretion in the urine, as suggested by the presence of non-butanol soluble urinary iodide. The presence of large amounts of the iodoprotein in the serum does not compensate for the lack of thyroxine. Perhaps the iodothyronines in it are metabolized wherever the iodoprotein is broken down, and are therefore not available to the general circulation. Also, its metabolic "inactivity" could be related to urinary excretion of a large portion of the compound.

As yet it is not known whether the urinary component is identical with or a fragment of the serum component. The finding of MIT, DIT and thyroxine in the urine suggests that this iodinated "polypeptide" is further broken down after excretion. Dialyzability of the urinary component suggests a relatively small size.

A plausible hypothesis is that the butanol insoluble serum component is a normal complex formed in the pathway of synthesis of thyroglobulin, or an abnormal synthetic product closely related to thyroglobin. The abnormal component is apparently not readily stored in the thyroid follicle. Another possibility is that this molecule represents the product of a normal alternative thyroidal metabolic pathway, which is accentuated in hyperplasia. It has been reported that dogs fed propylthiouracil have thyroidal iodoproteins of greater than normal solubility [*10*]. However, no such protein has been observed in the serum of patients with Graves' disease. It is also possible that this abnormal material is a fragment of thyroglobulin produced by abnormal thyroidal proteolytic enzymes. The virtual absence of thyroglobulin in the gland of patient C. C. (Case IV) is evidence against this hypothesis, as thyroglobulin should have been present in the follicles if there was a defect in thyroglobulin proteolysis.

It is possible that the syndrome herein

presented shares a common metabolic abnormality with other thyroid disease states. An abnormal protein identical in all respects tested has been found in the serum of patients with carcinoma of the thyroid [*11*]. No explanation for this finding has yet related it to the pathogenesis of the tumors, but most likely it is a secretion product of the cancer. The hypothesis could be raised that the component is etiologically related to tumor formation, but it seems highly unlikely that all the patients with cancer in whom the abnormal compound has been found suffered originally from a congenital defect in thyroid hormone synthesis.

Recently in this laboratory, studies on some patients with adenomatous colloid goiter have revealed the presence of up to 20 per cent $NBEI^{131}$ in their serum, and a "prethyroglobulin" protein in thyroid saline extracts [*12*]. Thus the defect in the group with congenital metabolic defect may represent an accentuation of a problem present in adenomatous colloid goiter. These two diseases could represent the homozygous and heterozygous states of a common genetic defect in the synthesis of thyroglobulin. No direct proof for this hypothesis is available, and indeed three of our subjects had no familial thyroid disease.

SUMMARY

Clinical and laboratory data on five patients suffering from one variety of congenital hypothyroidism with goiter are reported, and similar cases from the literature are reviewed. In these patients hypothyroidism and goiter develop early in life. They may suffer permanent physical and mental retardation unless the disorder is detected and adequate replacement therapy is given. There is increased RaI^{131} uptake by the thyroid and no release of I^{131} upon administration of potassium thiocyanate. The deiodinase activity is normal.

An abnormal iodinated polypeptide or protein is secreted by the thyroid. It is detected by its failure to extract into n-butanol from acidified serum. A similar complex is present in the urine. Abnormalities in the distribution of I^{131} in the thyroid subcellular particulate fractions and in the thyroidal proteins have been detected in the two glands which have been available for analysis.

This syndrome may be the expression of a congenital defect in thyroglobulin synthesis. Similar observations in certain patients with adenomatous colloid goiter suggest that this type of congenital goiter and a type of adenomatous colloid goiter may represent different levels of expression of a common genetic defect.

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Review

The Serum Proteins in Health and Disease*

Filter Paper Electrophoresis

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Since the early descriptions by Tiselius [*1–4*] of the electrophoretic separation of proteins by the moving boundary technic, and later the more practical method of filter paper electrophoresis described by Wieland and Fischer [*5*], and Turba and Enenkel [*6*] in Germany, Cremer and Tiselius [*7*] in Sweden and Durrum [*8*] in America, the intensive study of the serum proteins in various diseases has been reflected in the vast amount of literature now available. The relative simplicity of filter paper electrophoresis, together with the development of rapid methods of recording and quantitating the results, has given great impetus to this procedure and has made possible its application on a broad scale to the study of serum, urinary and other proteins. Early reports dealt mainly with problems concerned in the standardization of the technic [*9–12*]. Values for albumin were found to be reduced because of binding of the protein to the paper along the path of migration. Offsetting this to some extent was the observation that albumin has a greater affinity for some of the dyes that are commonly used than do the various globulin components, although this is less evident with amido-schwarz than with other anionic dyes [*9*]. In the moving boundary technic, the protein-bound lipid and carbohydrate are measured as well, so that values for some of the globulin components, especially the beta globulin, are higher in lipemic serums than by paper electrophoresis [*10–12*]. It must be stressed, therefore, that the values obtainable by available methods are not absolute. As Gutman [*13*] and others have indicated, the concept of the purity of proteins is relative, and has meaning only with reference to the method and assumptions used in studying the substances which are fractionated.

Comprehensive analyses of serum protein changes in various diseases, as measured by free electrophoresis, have been recorded by a number of authors [*13–17*]. However, reports describing the changes observed by electrophoresis on filter paper have been confined to a large extent to single or related diseases, although a few authors have described observations on larger groups of diseases as determined by a standardized technic [*18–22*]. Perhaps the most comprehensive of these has been the report of Jencks et al. [*22*]. The present report deals with such a study.

METHODS

In most instances the total protein of the serum was determined by the biuret technic [*23*] standardized with bovine serum albumin, but in turbid serums by micro-Kjeldahl nitrogen determination. In the electrophoretic separation, strips of No. 1 Whatman filter paper, supported on horizontal plastic frames, were saturated with a veronal buffer of ionic strength 0.05 at pH 8.6. After ten minutes for equilibration in a plastic cabinet, 0.01 ml. of serum was spread across the width of the paper at the negative pole. A current of 4.5 milliamperes and 90 to 100 volts was then applied for sixteen hours. The strips were air dried and afterwards placed in an oven at 90°c. for thirty minutes. The proteins were stained with amido-schwarz for ten minutes, followed by removal of the

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excess dye with 50 per cent methanol and 10 per cent glacial acetic acid.

In urine, the protein was precipitated with 10 per cent trichloracetic acid, washed and reconstituted in normal saline solution. Total urinary protein, in gm. per 100 ml., was determined by the biuret method to indicate the degree of concentration necessary for electrophoretic purposes. Before electrophoresis, the urine was dialyzed in a cellophane membrane against a 25 per cent solution of polyvinylpyrrolidone, and after suitable concentration was treated in the same manner as the serum.

A specially designed electronic scanning device [*24*], employing the principle of reflected light and standardized against elution determinations, was used for the quantitative evaluation of the filter paper strips. In this apparatus the basic system includes a well stabilized power supply, an optical system and a highly polished metal drum on which is fastened the stained filter paper strip. As the drum is rotated (3,000 r.p.m.), the paper is illuminated with a narrow beam of light (0.5 mm. × 38 mm.) and the reflected light from the paper is collimated on to a photomultiplier cell. The current which is generated is passed through a synchronizing circuit in order to obtain a steady picture of the distribution curve on a cathode ray tube. The latter is used only as a visual indicator during the operations involved in the actual evaluation.

To this basic system has been added a correcting exponential amplifier (*cf.* Beer-Lambert law), the output of which is fed into an electronic integrator and also into the cathode ray tube, in order to produce the ordinate or base line, corresponding to those regions of the paper strip where no protein is present. By this method the distribution pattern in normal serum is shown as a smooth, sharply defined curve, with five clearly separated components (albumin; alpha^1, alpha^2, beta and gamma globulin). (Fig. 1.) The curve represents in effect the summation of approximately twenty-five scannings per second. Since the Beer-Lambert law has been found to apply, the height of the curve represents directly the dye concentration at any given point along the filter paper without further correction. Two phantastrons permit a rapid evaluation of the area enclosed under the whole, or any portion of the distribution curve which may be selected for electronic integration. For record purposes, the electrophoretic curve is photographed immediately on polaroid film, but the quantitation of the individual peaks is read directly from a meter, either in terms of per cent of the total or as gm. per 100 ml.

The results will be reported in gm. per 100 ml., since this gives a more useful indication of the absolute changes in the individual protein fractions. Data reported as per cent of the total protein are satisfactory when there is no great deviation from the normal pattern, but the presence of a marked increase in any one component will give abnormally low and misleading values for all the remaining fractions, and vice versa.

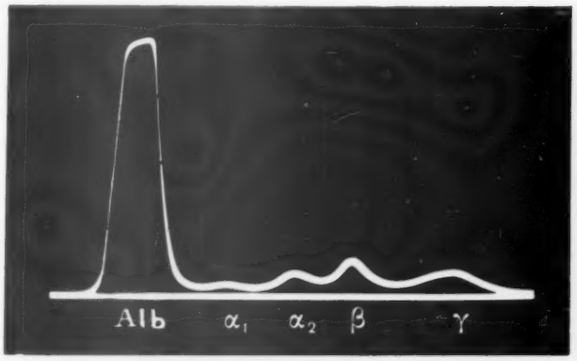


FIG. 1. Normal electrophoretic pattern of the serum proteins in a healthy subject.

MATERIAL

In the past two years more than 3,000 electrophoretic determinations have been reviewed, derived largely from patients in Sunnybrook (Veterans') Hospital and the Toronto General Hospital. Most of the patients selected for this report were individually examined by two of us (M. M. and M. A. O.), and in all instances the clinical diagnosis verified. When an accurate diagnosis could not be made or was in doubt, the data were not included in the present review.

To be reported are data on 100 normal persons, together with a broad spectrum of patients with rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polyarteritis nodosa, dermatomyositis, rheumatic fever, ankylosing spondylitis, Reiter's syndrome, gout, infectious hepatitis, portal cirrhosis, chronic "lupoid" hepatitis, sarcoidosis, ulcerative colitis, glomerulonephritis, nephrotic syndrome, Kimmelstiel-Wilson's syndrome, leukemias, lymphomas, multiple myeloma, agammaglobulinemia and a number of other diseases. As will be apparent, some of these diseases are associated with characteristic serum protein patterns which while not specific may be of distinct value to the clinician in the diagnosis and assessment of the clinical state. Some of the more important diseases showing distribution patterns which deviated significantly from the normal will be illustrated graphically, with representative distribution curves.

RESULTS

Normal Healthy Adults. In some reports, normal values have been determined on pooled human serum, or on serum taken from hospitalized patients suffering from a variety of minor illnesses in whom no specific diagnosis was made. For the purpose of this study the data for the

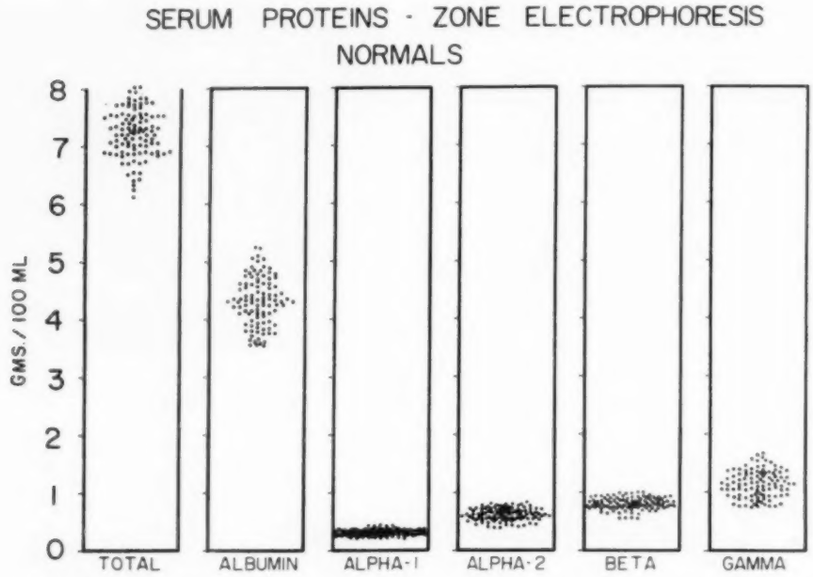


FIG. 2. Distribution of the serum protein fractions in 100 healthy subjects.

normal group were obtained from 100 active, young, white adults, between the ages of eighteen and forty-five years, who were either medical students, internes, nurses or laboratory technicians in good health. It was considered that these values would represent as nearly as possible the normal distribution of the serum proteins in the healthy state. Each person was questioned at the time the fasting sample was taken as to any present illness, allergic state, therapy or past illness which might have affected the serum protein pattern. Jencks et al. [*22*] have shown that there is no significant change in the serum proteins with advancing age or in the sexes, although racial variations do occur [*25*].

The results for the normal group, shown in scattergram fashion in Figure 2, would indicate that the total quantity of the serum proteins and the concentration of the individual fractions remain fairly constant within a relatively narrow range (total protein 6.4 to 8.1; albumin 3.5 to 5.2; alpha^1 0.2 to 0.4, alpha^2 0.4 to 0.8, beta 0.6 to 1.0, and gamma globulin 0.7 to 1.6 gm. per 100 ml.). In subsequent scattergram charts for the various disease states, the normal range (mean ± 2 standard deviations) is shown as a shaded area. The mean values and standard deviations for the various fractions, in the normal group and in different diseases, are shown in Table I.

Rheumatoid Arthritis. The pattern in rheumatoid arthritis is not specific. It frequently shows some reduction of the albumin together with an increase in the alpha^2, beta and/or gamma globulin fractions [*13,17,26,27*]. (Figs. 3 and 4, Table I.) However, these changes may be entirely absent in patients with active disease. Analysis of the records of 150 patients with rheumatoid arthritis has shown the albumin fraction to be reduced in 55 per cent, the alpha^2 increased in 42 per cent, the beta increased in 13 per cent and the gamma globulin increased in 37 per cent of the patients. Although the elevation of the alpha^2 globulin has been reported to be an early change in rheumatoid arthritis [*17*], it was frequently observed to persist as the only abnormality in patients who had rheumatoid arthritis for many years. In thirty-eight patients, or 25 per cent of the group, the distribution pattern remained completely within normal limits. The highest levels for gamma globulin appeared to occur with severe and continued activity of the disease process [*27*]. With suppressive steroid therapy, the gamma globulin tended to decrease [*17,27,28*] and in some patients returned to normal levels. Rarely, it was suppressed to subnormal values, in one instance to 0.50 gm. per 100 ml.

A positive reaction to the L.E. test was demonstrated in fifteen of the patients with rheumatoid arthritis; seven of these occurred in patients who had severe systemic disease [*29*], with visceral involvement in addition to the classic signs of established chronic rheumatoid arthritis (subcutaneous nodules and peripheral joint deformities of long standing), the remaining

eight patients showed only the characteristic changes of chronic rheumatoid arthritis, often accompanied by the presence of juxta-articular rheumatoid nodules, but without evidence of visceral disease. The majority of the patients with a positive L.E. phenomenon had abnormal serum protein patterns with elevation of the alpha^2 and gamma globulin fractions. A positive reaction to the L.E. test was demonstrated in two patients with rheumatoid arthritis who were admitted to the Surgical Service for treatment of chronic leg ulcers. Both had gross joint deformities with continued active disease for over thirty years. In one of these patients only a moderate reduction of the albumin was found, while the second had markedly elevated levels of gamma globulin. Mention will be made later of two patients not included in the present group of 150 patients, one with juvenile rheumatoid arthritis and so-called "agammaglobulinemia," and the other with Felty's syndrome, in whom the electrophoretic strip showed an abnormal protein constituent. (See Case VI in section on "Other Diseases with Abnormal Protein Components.")

Lupus Erythematosus. As has previously been reported with free electrophoresis [*17,30*], the distribution pattern in acute systemic lupus erythematosus was very similar to that of rheumatoid arthritis. (Figs. 5 and 6, Table I.) Here again the pattern was completely within the normal range in 14 per cent of the patients

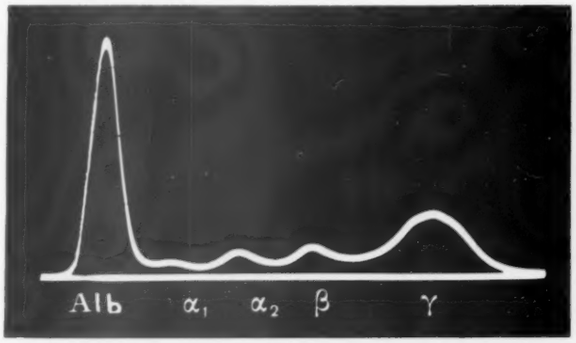


FIG. 3. Representative electrophoretic pattern of the serum proteins in a patient with rheumatoid arthritis.

in the presence of active disease. Analysis of the data in thirty-six patients with acute systemic lupus erythematosus showed the albumin to be reduced in 47 per cent, the alpha^2 increased in 33 per cent, the beta increased in 11 per cent and the gamma globulin increased in 58 per cent of the patients. Three of the low values for albumin occurred in patients who had the clinical picture of nephrotic syndrome with gross proteinuria and generalized edema. These patients will be discussed separately. On the whole, the levels for the alpha^2 and beta globulins tended to be somewhat lower in patients with systemic lupus erythematosus than in patients with rheumatoid arthritis, while the gamma globulin levels tended to be somewhat higher. Serial determinations of the serum proteins indicated that when the disease process was

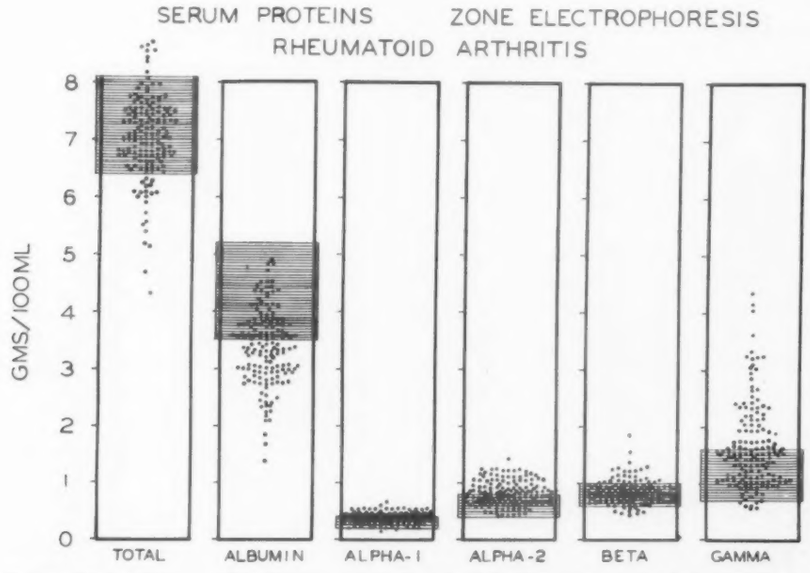


FIG. 4. Distribution of the serum protein fractions in 150 patients with rheumatoid arthritis.

TABLE 1

SERUM PROTEIN DISTRIBUTION IN HEALTHY SUBJECTS AND IN SUBJECTS WITH VARIOUS DISEASES

Disease	Value	Subjects (no.)	Total (gm. per 100 ml.)	Albumin (gm. per 100 ml.)	Alpha[1] (gm. per 100 ml.)	Alpha[2] (gm. per 100 ml.)	Beta (gm. per 100 ml.)	Gamma (gm. per 100 ml.)
	(Mean)	**100**	**7.22**	**4.32**	**.32**	**.62**	**.80**	**1.15**
	(S.D.)	**...**	**.42**	**.43**	**.05**	**.11**	**.10**	**.23**
Subjects with Rheumatic Diseases								
Rheumatoid arthritis	Mean	150	7.06	3.36	.37	.81	.85	1.66
	S.D.		.76	.65	.09	.21	.21	.74
	p		None	.001	.001	.001	.001	.001
Systemic lupus erythematosus	Mean	36	6.99	3.31	.35	.75	.78	1.95
	S.D.		1.13	.77	.09	.18	.23	.81
	p		None	.001	.02	.001	None	.001
Discoid lupus erythematosus	Mean	7	7.18	3.86	.35	.74	.88	1.36
	S.D.		.54	.33	.05	.18	.17	.36
	p		None	.01	None	.01	.001	.05
Scleroderma	Mean	20	7.45	3.61	.32	.64	.83	1.66
	S.D.		.54	.91	.11	.21	.27	.70
	p		.05	.001	None	None	None	.001
Dermatomyositis	Mean	8	6.86	3.46	.31	.85	.82	1.41
	S.D.		1.01	.36	.05	.31	.36	.69
	p		.05	.001	None	.001	None	.001
Polyarteritis	Mean	6	6.86	2.76	.45	.84	.78	1.97
	S.D.		.95	1.05	.14	.37	.16	.63
	p		None	.001	.001	.001	None	.001
Undifferentiated "collagen disease"	Mean	35	7.05	3.43	.37	.80	.82	1.62
	S.D.		.88	.89	.07	.24	.19	.82
	p		None	.001	.001	.001	None	.001
Rheumatic fever	Mean	15	6.90	3.67	.33	.78	.75	1.35
	S.D.		.48	.32	.08	.26	.16	.28
	p		.01	.001	None	.001	None	.01
Gout	Mean	49	7.25	4.17	.32	.70	.93	1.14
	S.D.		.55	.49	.08	.20	.19	.20
	p		None	None	None	.01	.001	None
Marie-Strümpell spondylitis	Mean	113	7.36	4.16	.32	.80	.86	1.23
	S.D.		.50	.41	.06	.16	.16	.41
	p		None	None	None	.001	.01	None
Reiter's syndrome	Mean	8	7.04	3.44	.39	1.08	.90	1.23
	S.D.		.42	.58	.07	.40	.22	.21
	p		None	.001	.001	.001	.001	None
Subjects with Liver Disease and Sarcoidosis								
Portal cirrhosis	Mean	40	7.14	3.21	.34	.58	.89	2.14
	S.D.		.70	.73	.11	.25	.32	.85
	p		None	.001	None	None	.001	.001
Chronic (lupoid) hepatitis	Mean	5	9.99	2.54	.24	.60	.52	6.31
	S.D.		1.70	.81	.09	.11	.15	1.82
	p		.001	.001	.01	None	.001	.001
Infectious hepatitis	Mean	7	7.44	3.69	.35	.66	.92	1.80
	S.D.		.69	.56	.08	.17	.20	.50
	p		None	.05	None	None	.001	.001
Sarcoidosis	Mean	9	7.03	3.78	.34	.70	.89	1.31
	S.D.		.81	.70	.04	.17	.22	.48
	p		None	.001	None	.05	.01	None
Subjects with Gastrointestinal Disorders								
Crohn's disease	Mean	2	5.23	2.81	.33	.59	.61	.87
	S.D.		1.12	1.12	.03	.16	.01	.21
	p		.001	.001	None	None	.02	.001
Ulcerative colitis	Mean	2	6.21	2.53	.46	1.14	.78	1.29
	S.D.		.66	.01	.0	.10	.22	.53
	p		.02	.001	None	.001	None	None

TABLE 1 (*Continued*)

SERUM PROTEIN DISTRIBUTION IN HEALTHY SUBJECTS AND IN SUBJECTS WITH VARIOUS DISEASES

Disease	Value	Subjects (no.)	Total (gm. per 100 ml.)	Albumin (gm. per 100 ml.)	Alpha[1] (gm. per 100 ml.)	Alpha[2] (gm. per 100 ml.)	Beta (gm. per 100 ml.)	Gamma (gm. per 100 ml.)
Subjects with Renal Diseases								
Nephrotic syndrome	Mean	14	4.35	1.39	.23	1.48	.71	.56
	S.D.		.50	.51	.09	.36	.14	.16
	p		.001	.001	.001	.001	.001	.001
Acute glomerulonephritis	Mean	8	6.47	3.13	.38	.83	.81	1.33
	S.D.		1.01	.92	.19	.35	.23	.55
	p		.001	.001	.02	.001	None	None
Subacute glomerulonephritis	Mean	9	5.82	2.76	.36	.82	.74	1.11
	S.D.		1.22	.87	.06	.19	.14	.57
	p		.001	.001	.01	.001	None	None
Chronic glomerulonephritis	Mean	9	6.31	3.27	.36	.75	.68	1.25
	S.D.		1.15	.95	.07	.25	.20	.62
	p		.001	.001	.05	.001	.01	None
Kimmelstiel-Wilson's syndrome	Mean	13	5.88	2.87	.33	.82	.80	1.02
	S.D.		.62	.68	.10	.24	.27	.54
	p		.001	.001	None	.001	None	None
Subjects with Leukemias and Lymphomas								
Chronic lymphatic leukemia	Mean	12	6.31	3.75	.44	.74	.70	.67
	S.D.		.58	.59	.48	.25	.24	.14
	p		.001	.001	.001	.01	.01	.001
Subacute lymphatic leukemia	Mean	2	5.87	2.96	.47	.73	.68	1.02
	S.D.		.71	.17	.08	.36	.28	.63
	p		.001	.001	.001	None	None	None
Chronic myeloid leukemia	Mean	2	5.51	3.00	.50	.68	.53	.78
	S.D.		.68	.01	.13	.05	.18	.33
	p		.001	.001	.001	None	.001	None
Acute leukemia	Mean	9	6.68	3.60	.48	.81	.70	1.15
	S.D.		.70	.38	.10	.33	.33	.38
	p		.001	.01	.001	.001	.05	None
Lymphoma	Mean	9	7.60	3.19	.33	.65	.75	2.67
	S.D.		2.25	1.11	.07	.28	.24	2.97
	p		None	.001	None	None	None	.001
*Subjects with Multiple Myeloma**								
Multiple myeloma	Mean	50	8.38	3.37	.35	.69	.65	.48
	S.D.		1.62	.77	.03	.30	.15	.26
	p		.001	.001	.01	.05	.001	.001
Subjects with Agammaglobulinemia								
Agammaglobulinemia	Mean	3	5.59	3.88	.37	.59	.63	.11
	S.D.		.51	.76	.07	.33	.03	.06
	p		.001	None	None	None	.01	.001

NOTE: Figures in bold face type represent values in normal subjects.

* The abnormal protein constituents were not included in the statistical analysis of the individual fractions, but were included in the total protein. Their relative concentrations and positions are shown in Figure 16. (Mean—3.4 gm. per 100 ml. Range—0.25 to 7.46 gm. per 100 ml.)

suppressed with steroid therapy the gamma globulin decreased while the albumin usually increased [*30*], approximating or frequently returning to normal values during sustained remissions. As a rule in such instances the L.E. phenomenon could no longer be demonstrated. In one patient, however, although the gamma globulin level decreased to 0.45 gm. per 100 ml.

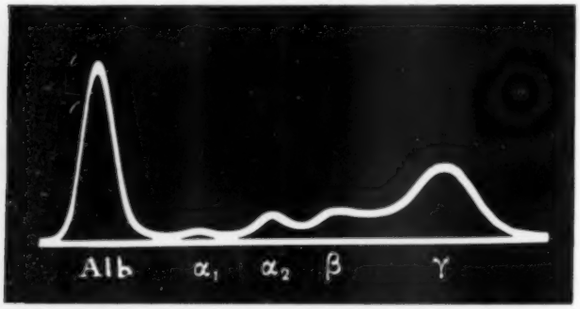


FIG. 5. Representative electrophoretic pattern of the serum proteins in a patient with systemic lupus erythematosus.

the reaction to the L.E. test remained weakly positive.

There were seven patients with chronic discoid lupus erythematosus. In four of these patients the protein values were normal. Two showed a slight elevation of the alpha^2 fraction and in the third there was a slight reduction in the albumin. Two patients showed a slight increase in the gamma globulin.

Other "Collagen Diseases." Similar but perhaps less marked changes in the serum protein pattern have been observed in persons with other diseases of the collagen group. (Table 1.) Of twenty patients with scleroderma, the most significant abnormalities were a moderate elevation of the gamma globulin level in nine patients and a slight reduction of the albumin in four patients. In eight patients with dermatomyositis an elevated gamma globulin level was observed in only three instances. There was some decrease in albumin in five patients and a significant increase in the alpha^2 fraction in four patients. The serum protein changes in six patients with polyarteritis consisted mainly of a moderate reduction of the albumin in five patients, an increase in the alpha^2 fraction in three patients and an increase in the gamma globulin in four patients. In one patient who has done very well clinically the pattern was only slightly abnormal, with some reduction of albumin. With steroid therapy over a period of a year this pattern has returned to normal. The changes observed in a group of thirty-five patients with undifferentiated connective tissue disorders were roughly comparable to those just described. (Table 1.)

Rheumatic Fever. There was no significant deviation from the normal pattern in eight of fifteen patients with active rheumatic fever. (Table 1.) A slight decrease in albumin and/or an increase in the alpha^2 and gamma globulin levels was observed in seven patients. The highest value obtained for gamma globulin was 2.12 gm. per 100 ml.

Gout. There was no distinctive pattern in patients with gout. (Table 1.) The distribution of the serum proteins in forty-nine patients showed a slight increase in the alpha^2 and a more distinct increase in the beta fractions in 25 and 28 per cent, respectively. The occurrence of an abnormality in the lipoprotein components is interesting in the light of the high incidence of

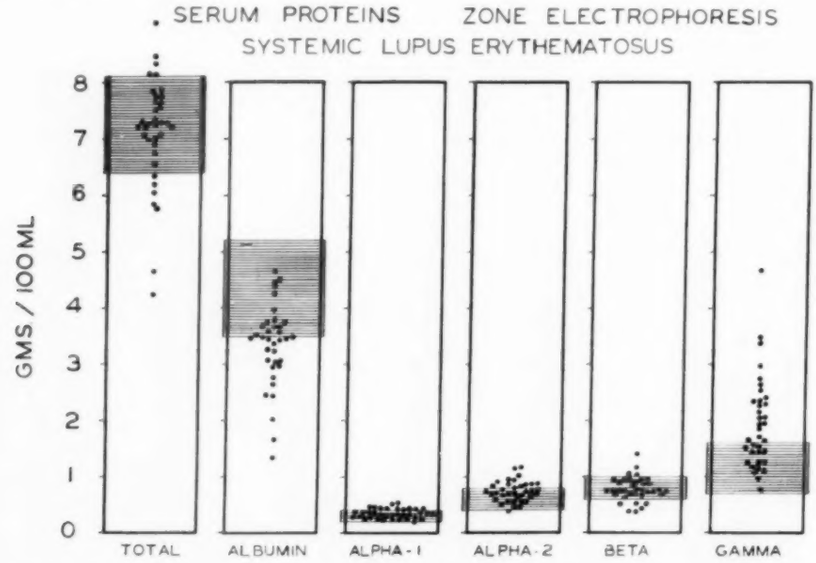


FIG. 6. Distribution of the serum protein fractions in thirty-six patients with systemic lupus erythematosus.

atherosclerosis in this disease and the frequent association of an elevated uric acid level in patients with atherosclerosis.

Marie-Strümpell Spondylitis. Analysis of the data on 113 patients with Marie-Strümpell spondylitis did not show striking deviation from normal. (Table I.) Nevertheless, 36 per cent of the patients had some elevation of the alpha^2 fraction, 10 per cent an increase in the beta fraction and 15 per cent a minor increase in the gamma fraction, along with some slight reduction of the albumin. In the occasional patient who showed a significant increase in gamma globulin, examination usually disclosed gross peripheral joint disease of long standing. Mention will be made later of one patient with ankylosing spondylitis, not included in the present group, whose serum showed an abnormal component having the characteristics of a cryoglobulin. (See Case VII in section on "Other Diseases with Abnormal Protein Components.")

Reiter's Syndrome. The most significant abnormality in eight patients with Reiter's syndrome was an increase in the alpha^2 and beta fractions, with some reduction of the albumin, but only minor changes in the gamma globulin.

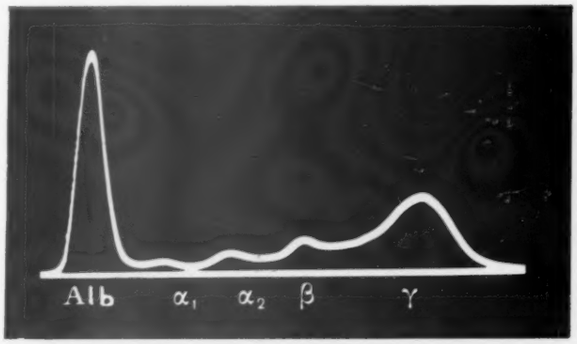


FIG. 7. Representative electrophoretic pattern of the serum proteins in a patient with portal cirrhosis.

(Table I.) In five patients the increase in the alpha^2 fraction was rather striking during the acute phase of the disease, reaching values up to 1.74 gm. per cent. Reiter's syndrome, ulcerative colitis and the nephrotic syndrome were the only diseases in which the mean values for alpha^2 globulin exceeded 1.0 gm. per 100 ml.

Chronic Liver Disease. The general pattern in patients with portal cirrhosis could not be distinguished from those just described for rheumatoid arthritis or systemic lupus erythematosus. (Figs. 7 and 8, Table I.) The most significant

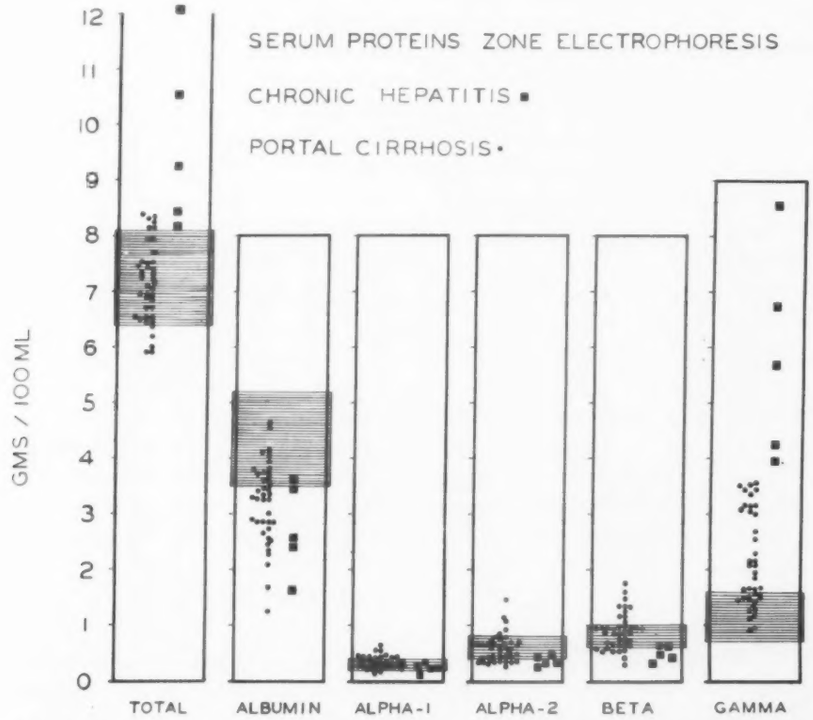
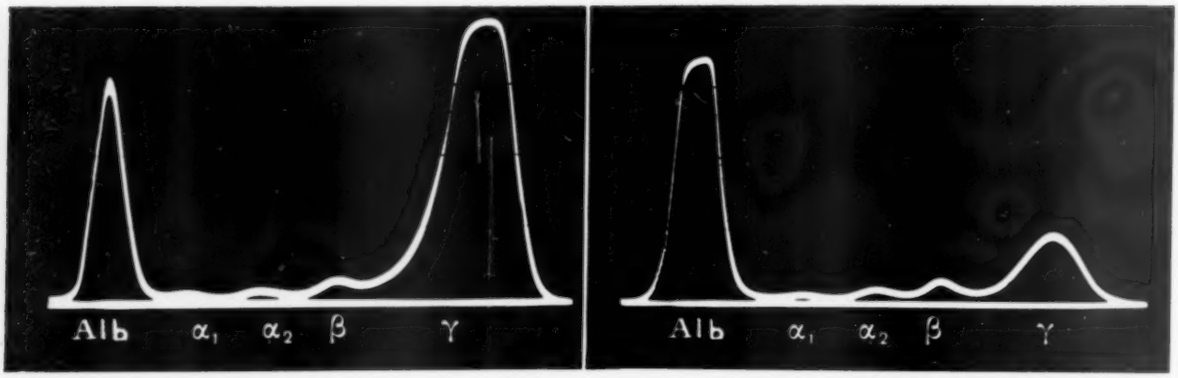


FIG. 8. Distribution of the serum protein fractions in forty patients with portal cirrhosis (dots), contrasted with five patients with chronic "lupoid" hepatitis (squares). Note the high values for total protein and the greatly increased gamma globulin in the latter group.



9a 9b

FIG. 9. Representative electrophoretic pattern of the serum proteins in a patient with chronic "lupoid" hepatitis; (a) before administration of steroid therapy, and (b) after three months of steroid therapy.

changes were a reduction of the albumin and an increase in the gamma globulin components [*13*], perhaps a little more pronounced than in the "collagen diseases." Analysis of data on forty patients with portal cirrhosis showed the albumin to be reduced in 60 per cent of the patients, the lowest value being 1.2 gm. per 100 ml. The alpha^2 fraction was increased in 10 per cent, the beta in 10 per cent and the gamma globulin increased in 60 per cent of the patients.

However, in a smaller proportion of patients, five young women with a chronic hepatitis or postnecrotic cirrhosis of many months' duration, with jaundice, ascites, joint symptoms, amenorrhoea and a positive L.E. phenomenon (so-called lupoid hepatitis) [*31–35*], the changes were much more profound. (Figs. 8 and 9a, Table I.) The serums of these patients showed a very high total protein, the mean value exceeding even that of the multiple myeloma group. This change was due entirely to an increase in the gamma globulin, which appeared as a broad band in concentrations varying from 4.0 to 8.6 gm. per 100 ml.* In three cases there was a marked reduction of the albumin fraction. Steroid therapy in this group of patients appeared to be of distinct clinical benefit. It resulted in reversal of the abnormal pattern toward a more normal picture (Fig. 9b) in all instances although none became entirely normal. While some increase in the gamma globulin usually persisted, the reaction to the L.E. test eventually became negative in three of the patients. The marked contrast between these two groups of patients with chronic liver disease was very impressive.

Infectious Hepatitis. There were seven patients with infectious hepatitis. The serum proteins in this disease showed a slight reduction in the albumin in one patient, a small increase in the alpha^2 and beta fractions in one patient each, and an increase in the gamma globulin in five patients. These changes were less striking than those observed in patients with chronic liver disease. (Table I.)

Crohn's Disease and Ulcerative Colitis. In one patient with Crohn's disease the pattern was normal while in another there was only a marked decrease in the albumin fraction. This is in contrast to two patients with ulcerative colitis who showed a marked reduction of the albumin and an increase in the alpha^2 globulin.

Sarcoidosis. It was surprising to find that the gamma globulin was significantly increased in only one of nine patients with proved sarcoidosis. One patient showed an increase in the alpha^2 and three patients an increase in the beta fraction.

Miscellaneous Diseases. It is not possible to discuss individually all the diseases in which serum protein changes of the general character of those described may be encountered. These include certain acquired hemolytic anemias, idiopathic thrombocytopenic and various types of non-thrombocytopenic purpuras, allergic and hyperimmune or reactive disease states, certain chronic infective diseases, diseases associated with hyperglobulinemia and the presence of cryoglobulins or macroglobulins in varying amounts, and sometimes obscure illnesses in which a specific diagnosis could not be made even after postmortem examination. In one patient with idiopathic thrombocytopenic purpura,

* Since this report was submitted, the serum of one patient suffering from systemic lupus erythematosus but with no evidence of liver disease, exhibited a similar high concentration of gamma globulin, amounting to 6.3 gm. per 100 ml.

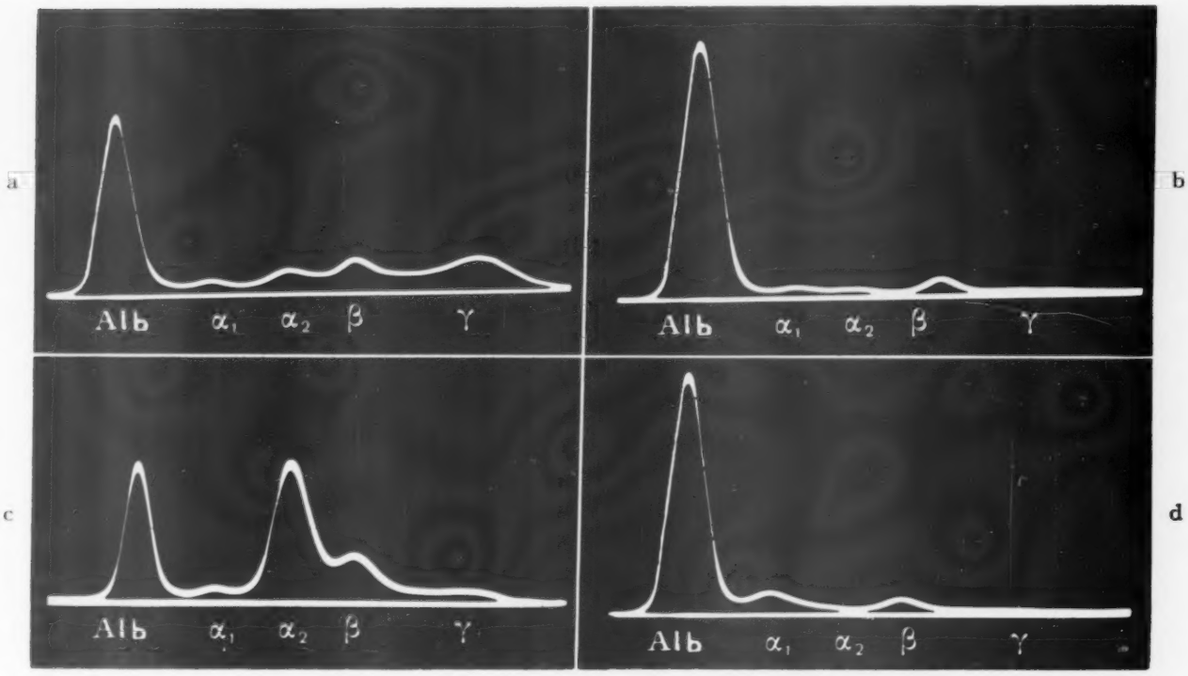


FIG. 10. Representative electrophoretic protein patterns of (a) serum and (b) urine, in a patient with systemic lupus erythematosus and generalized edema, and (c) serum and (d) urine, in a patient with nephrotic syndrome due to glomerulonephritis.

the gamma globulin was increased to 4.75 gm. per 100 ml., and in one patient with leprosy to 2.07 gm. per 100 ml.

Nephrotic Syndrome. The recognition of systemic lupus erythematosus may sometimes be difficult when this disease presents with the clinical picture of a nephrotic syndrome. The serum pattern in three such patients has shown only a reduction in the serum albumin (Figs. 10a and 11), the remaining fractions being relatively normal. None showed a significant increase in the alpha^2 fraction. While the gamma globulin was lower than the mean for the whole group of patients with systemic lupus erythematosus, it did not drop below the normal range. The pattern of the proteins in the urine consisted largely of albumin with small traces of other components. (Fig. 10b.)

In fourteen patients, all adults with the nephrotic syndrome believed to be due to glomerulonephritis, the serum pattern was quite different. In this group there was a consistent increase in the alpha^2 fraction, and a marked reduction in the albumin fraction in all patients. (Table I, Figs 10c and 11.) The gamma globulin was significantly reduced in eleven patients, with low normal values in the remaining three patients. This pattern would appear to be highly characteristic of the nephrotic syndrome associated with glomerulonephritis [*36–38*]. It is of interest that the increased value for beta globulin reported in children with nephrosis by the free electrophoretic technic [*13,36,37*] was not observed in the present group, presumably because the increased lipides of the serum are not measured with filter paper electrophoresis. The urine protein pattern in these patients (Fig. 10d), however, was not much different from that occurring in patients with systemic lupus erythematosus (Fig. 10b) or other types of renal disease, with the exception of those accompanying multiple myeloma and related disorders. It would appear, therefore, that the serums of patients with the nephrotic syndrome due to glomerulonephritis tend to have higher levels of alpha^2 globulin and lower levels of gamma globulin, as compared with serums from patients with systemic lupus erythematosus and other diseases associated with renal involvement and proteinuria. While the number of patients is small, this difference appears significant and may be helpful in differentiating these diseases when they present with a nephrotic syndrome but without other characteristic signs. The pattern was, however, simulated in one patient with multiple myeloma

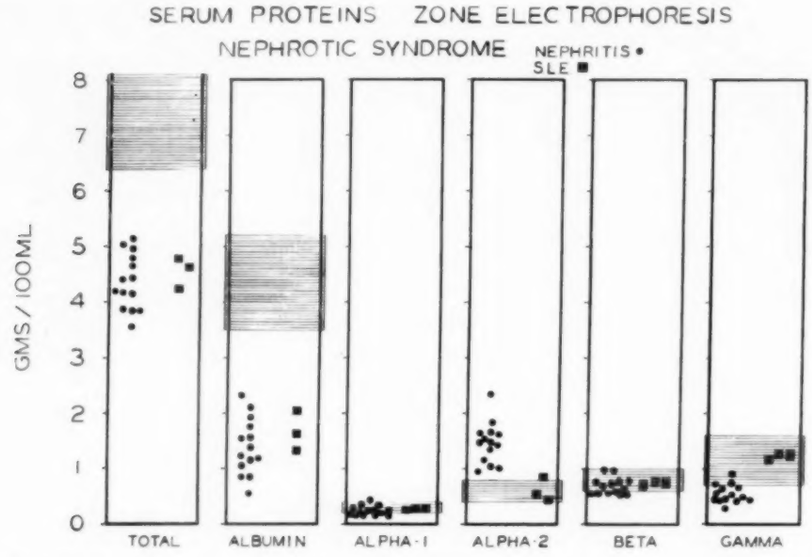


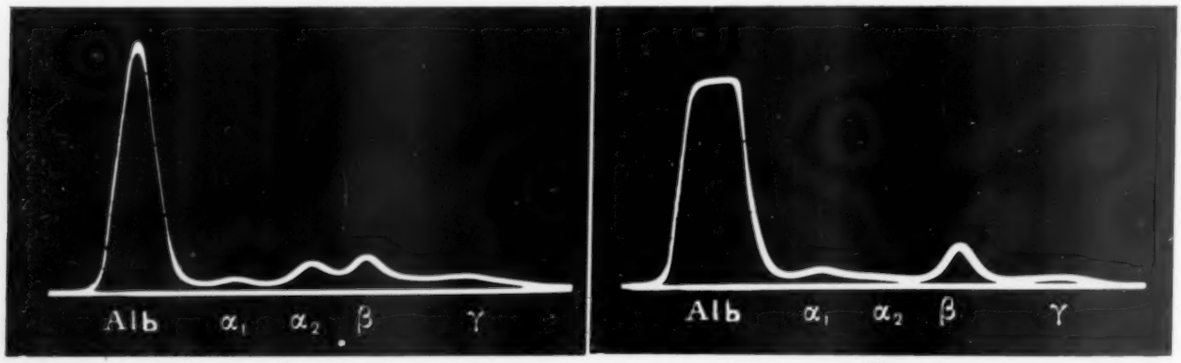
FIG. 11. Distribution of the serum protein fractions in fourteen patients with nephrotic syndrome due to glomerulonephritis (dots), contrasted with three patients with nephrotic syndrome due to systemic lupus erythematosus (squares). Note the increase in alpha^2 globulin and the decrease in the gamma globulin in the former group.

in whom the abnormal protein constituent of this disease appeared in the alpha^2 position, and also in one patient with amyloidosis and one with diabetes mellitus in whom there was marked proteinuria.

Glomerulonephritis. There were eight patients with acute glomerulonephritis, nine with subacute glomerulonephritis and nine with chronic glomerulonephritis. (Table 1.) In the majority of these cases there was some reduction in the total protein and albumin, which was most marked in the acute and subacute phases. Minor increases in the alpha^2 fraction were sometimes observed in all three groups, of the beta fraction only in the acute cases and of the gamma globulin in the acute and chronic cases, but only to a slight degree.

Kimmelstiel-Wilson Syndrome. In Kimmelstiel-Wilson's syndrome the serum and urine protein patterns were not distinctive. (Figs. 12a and 12b, Table 1.) Analysis of data on thirteen patients showed the total protein to be reduced in ten patients and the albumin to be reduced in eleven patients. Several exhibited a slight increase in the alpha^2 and beta fractions. The gamma globulin fraction was increased in one patient who was shown to have a staphylococcal septicemia. Two patients had subnormal values for gamma globulin.

Leukemia. There were twelve patients with



12a 12b

FIG. 12. Representative electrophoretic protein patterns of (a) serum and (b) urine, in a patient with Kimmelstiel-Wilson syndrome.

chronic lymphatic leukemia. (Table 1.) In addition to a reduction in the total protein and albumin, the striking change was a reduction in the gamma globulin in six patients. A history of repeated infections in three patients suggested the possibility of hypogammaglobulinemia. This was confirmed by electrophoretic studies and was demonstrated in one instance to be as low as 0.16 gm. per 100 ml. (Fig. 13.) One other patient received large amounts (20 to 30 cc. of a 15 per cent solution) of gamma globulin per month, over a nine-month period. In spite of this replacement therapy the level of gamma globulin continued to drop from 0.6 to 0.21 gm. per 100 ml. at the time of death. A less striking reduction of the gamma globulin to 0.58 gm. per 100 ml. was also observed in one of two patients with subacute lymphatic leukemia and to 0.55 gm. per 100 ml. in one of two patients with chronic myeloid leukemia. It was not observed in nine patients with acute leukemia. In all types of leukemia there was frequently some reduction in the total protein with a low albumin and slight increase in the alpha[1] and alpha[2] fractions. None of these patients showed significant hypergammaglobulinemia or the presence of abnormal protein constituents such as have been reported by others [*39,40*].

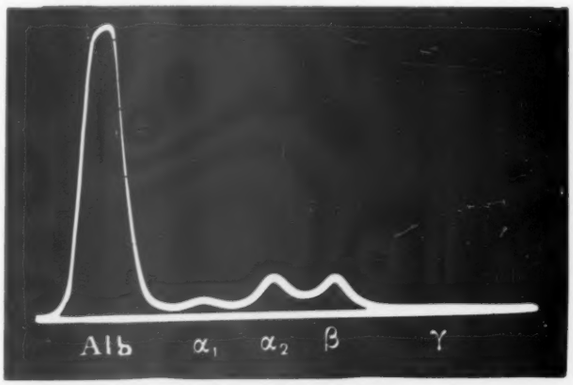
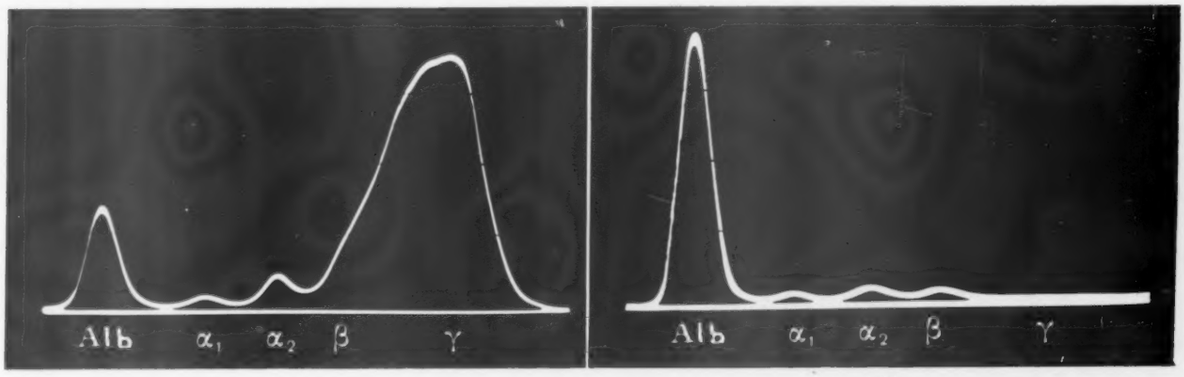


FIG. 13. Electrophoretic pattern of the serum proteins in a patient with chronic lymphatic leukemia and marked hypogammaglobulinemia.

Lymphoma. In nine patients with lymphomas of various types (Table 1), the albumin was reduced in four patients, with a slight increase in the alpha[2] fraction in two patients. Two patients showed a marked increase in the total protein which was due to a greatly elevated, broad gamma band, in amounts up to 7.85 and 7.9 gm. per 100 ml., respectively. (Fig. 14a.) One was a patient with Hodgkin's disease, the other with an undifferentiated malignant lymphoma. The latter showed a decrease in the gamma globulin to 2.4 gm. per 100 ml. after treatment with triethylene melamine and high voltage x-ray. Grassman has observed a similar increase in gamma globulin in a patient with giant follicle lymphoblastoma [*41*], and Arends et al. [*42*] have reported values of gamma globulin up to 3.5 and 3.9 gm. per 100 ml. The latter authors have suggested that some malignant cells may produce abnormal proteins which may circulate in the blood. One patient showed a significant hypogammaglobulinemia, with values for gamma globulin as low as 0.17 gm. per 100 ml. (Fig. 14b.) In none of the patients included in this group were abnormal protein constituents, such as are commonly seen in multiple myeloma, present although these have been described [*40,42*]. However, two patients not included in this group because they did not have the typical



14a 14b

FIG. 14. Electrophoretic patterns of the serum proteins in (a) patient with Hodgkin's disease showing a broad increase in the gamma globulin of a marked degree, and (b) patient with malignant lymphoma showing a marked hypogammaglobulinemia.

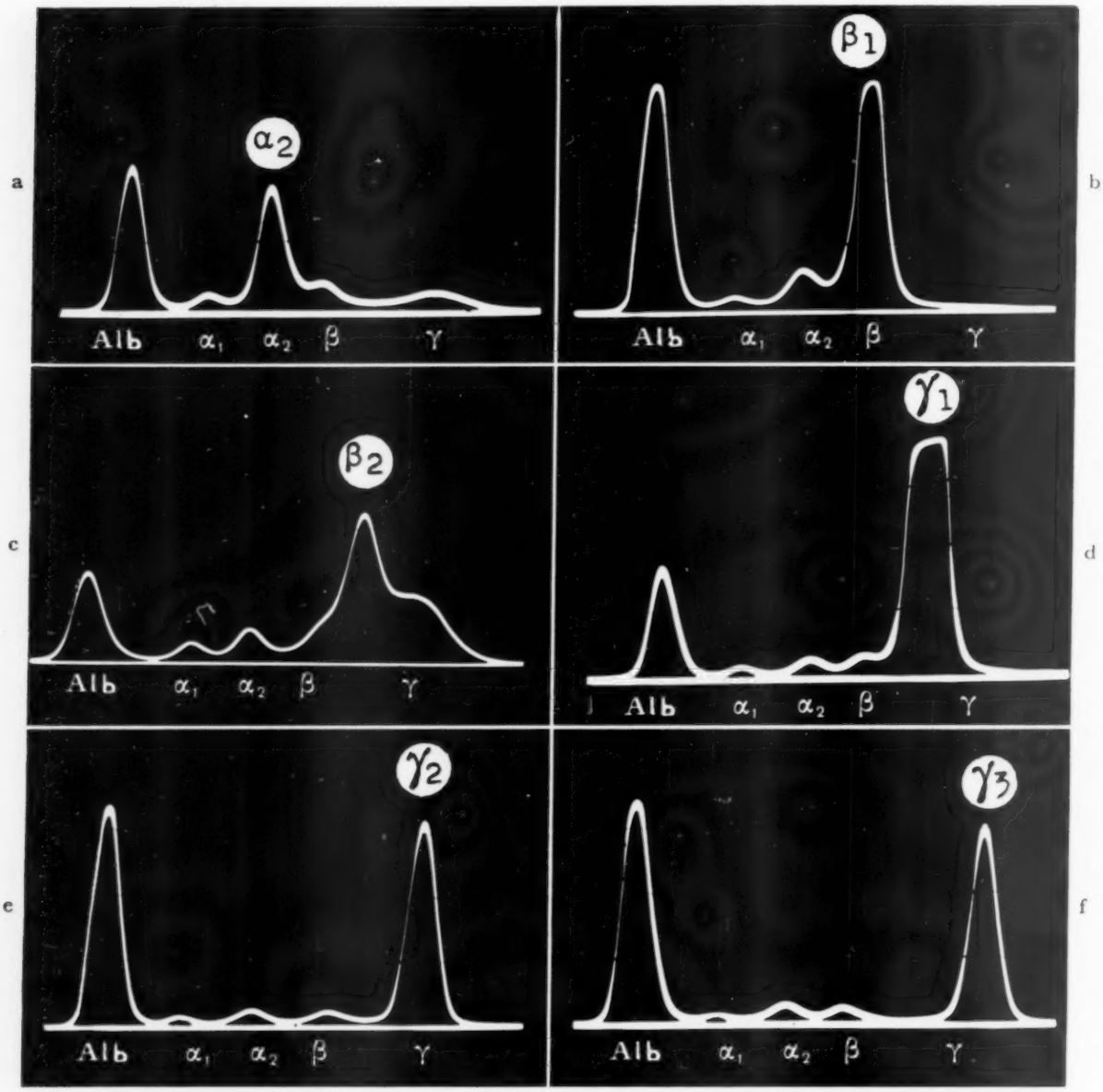


Fig. 15. Representative electrophoretic patterns of the serum proteins in six patients with multiple myeloma showing abnormal protein peaks in (a) alpha^2, (b) beta^1, (c) beta^2, (d) gamma^1, (e) gamma^2 and (f) gamma^3 positions.

findings of lymphoma, but who might conceivably be classed with this group (see section on "Other Diseases with Abnormal Protein Components" Cases II and III), did show abnormal protein constituents of the narrow band type.

Multiple Myeloma. Perhaps the most interesting of the whole group are the patients with multiple myeloma. Characteristically in this disease there is an abnormal protein which appears on the electrophoretic curve as a sharply defined peak [*13,43–50*]. Most commonly this occurs in the area of the gamma fraction, between the beta and gamma fractions, or in the beta fraction. Rarely, it has been reported as far forward as the alpha^2 fraction. Only one example of an alpha^2 band was encountered in the present study. (Fig. 15a.) When the abnormal band or peak occurred in the normal beta position it was designated beta^1. (Fig. 15b.) When the peak occurred between the normal beta and the gamma component, it was designated beta^2. (Fig. 15c.) Since the normal gamma globulin band is usually about twice as broad

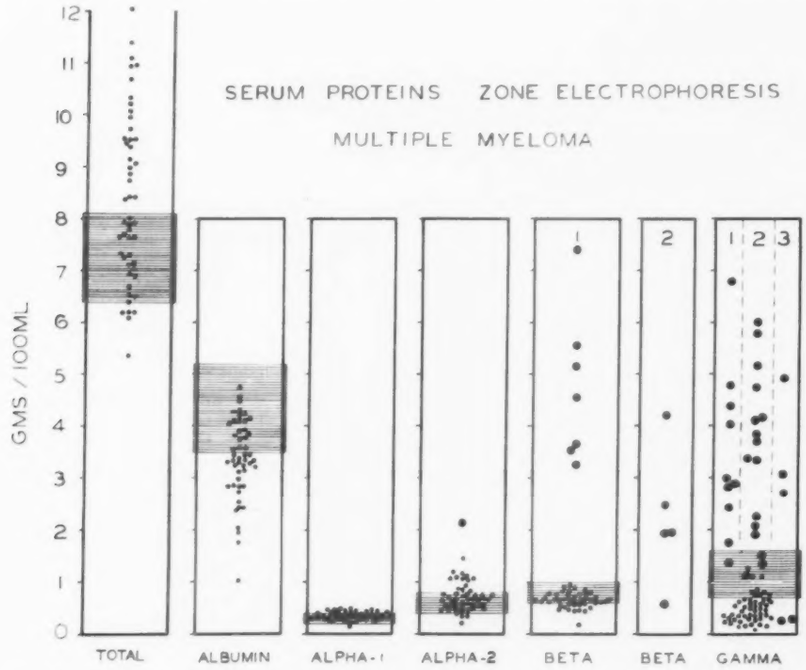


FIG. 16. Distribution of the serum protein fractions in fifty patients with multiple myeloma. The normal protein constituents are shown as small dots, while the relative position and concentration of the abnormal, myeloma proteins are indicated by the large dots.

as the other globulin fractions, it was possible to label the abnormal, narrow bands on the basis of their position in this fraction as gamma[1] (fast), gamma[2] (medium) or gamma[3] (slow moving) components. (Figs. 15d, 15e and 15f.)

Analysis of the serums of fifty patients with multiple myeloma associated with bone lesions and verified by biopsy of bone marrow or autopsy examination, showed such a band to be present in forty-four patients. These were located as follows: alpha[2], one patient; beta[1], seven patients; beta[2], five patients; gamma[1], ten patients; gamma[2], sixteen patients; and gamma[3], five patients. (Fig. 16.) The serum pattern was relatively normal or at most showed only slight reduction of the albumin and/or gamma globulin in five patients, with the abnormal band appearing in the urine. (Figs. 17a and 17b.) One additional patient exhibited a marked hypogammaglobulinemia, again with an abnormal protein in the urine. (Figs. 17c and 17d.)

The urines from thirty-two patients who showed proteinuria by the sulfosalicylic acid test were subjected to electrophoresis after suitable concentration. All showed a typical abnormal protein band, frequently but not always appearing in approximately the same position as the abnormal protein in the serum. In twenty-two instances this appeared as a dense band in the beta or gamma position together with smaller amounts of albumin and other globulins (Fig. 17f), while in ten instances only the abnormal protein appeared, as a dense band in the beta or gamma position without significant amounts of other components. (Figs. 17b and 17d.) It is significant that an abnormal protein band was demonstrated in the urine of all six patients in whom it was absent in the serum. Thus, an abnormal band was demonstrated either in the electrophoretic strip of the serum or urine, or in both, in all fifty patients with multiple myeloma. Comparable findings have been reported by other observers, although not always as consistently [*47,49*].

As Osserman [*51*] has indicated, the urine may be negative for Bence Jones protein yet positive on electrophoretic analysis, and this was true in the present group. Of the thirty-two patients in this study with abnormal proteins in the urine electrophoretically, only eleven had a positive reaction to the Bence Jones test. On the other hand, when the result of the Bence Jones test was positive in patients with multiple myeloma an abnormal band was always shown

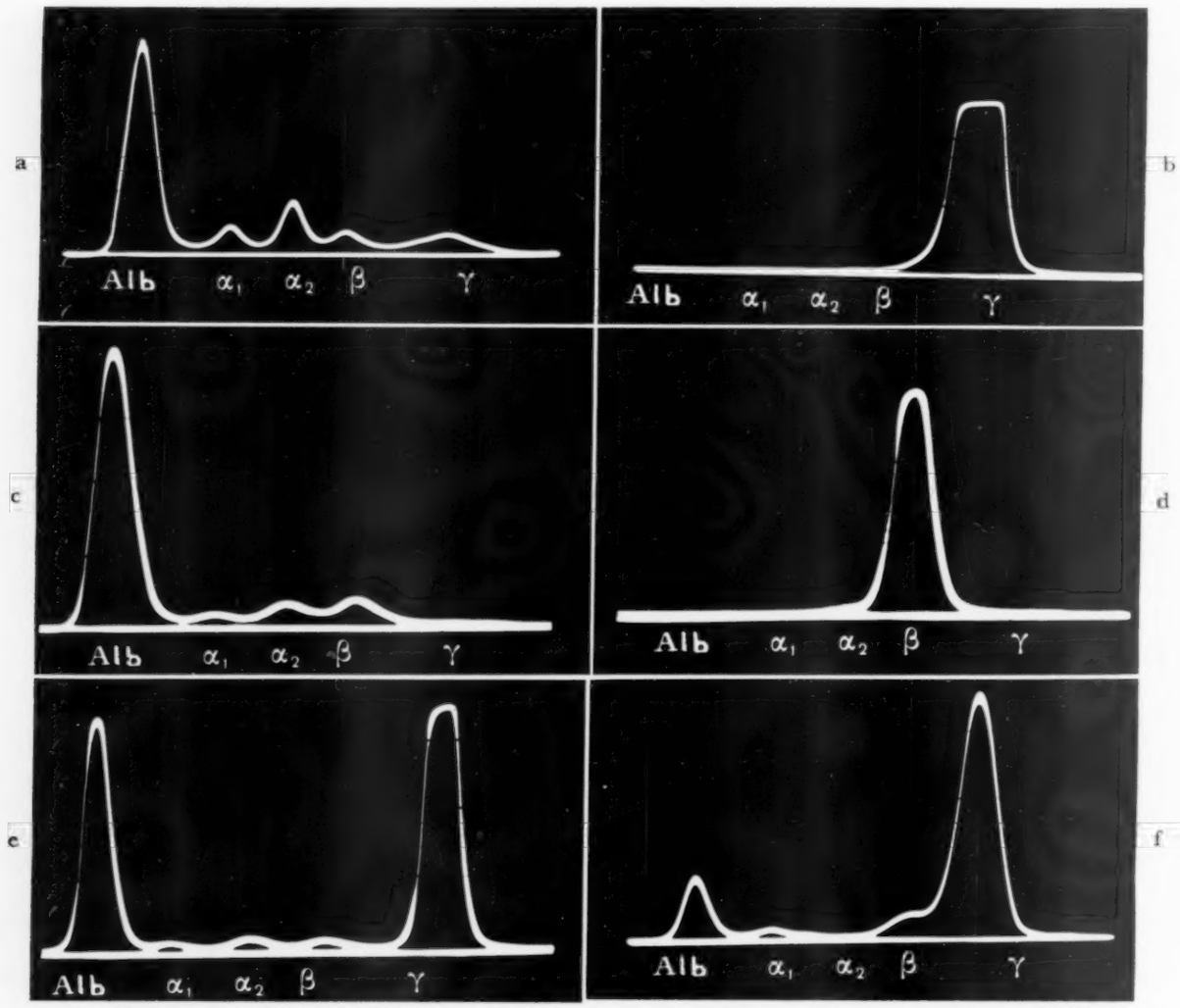


FIG. 17. Representative electrophoretic protein patterns in three patients with multiple myeloma illustrating (a) normal serum with (b) abnormal gamma constituent in the urine, (c) serum pattern showing marked hypogammaglobulinemia with (d) abnormal beta constituent in the urine, and (e) typical myeloma pattern in the serum with (f) abnormal gamma constituent in the urine together with smaller amounts of other normal fractions.

electrophoretically. It has often been emphasized that the Bence Jones test as performed in routine laboratories is subject to frequent false negative interpretation. As a screening diagnostic procedure, therefore, it is believed that electrophoretic analysis of the urinary proteins is more reliable than the Bence Jones test.

The origin of the abnormal serum protein and the abnormal urine protein, as well as their relationship to each other, has recently been discussed by Putnam [*52*]. It is generally believed that the abnormal urinary proteins are distinct and different from the myeloma proteins in the serum. Isotope studies of the rate of formation and turnover of these proteins indicate that the Bence Jones protein is rapidly formed and quickly excreted in the urine. The abnormal plasma component, however, contains much less activity and exhibits a much slower turnover. Therefore Putnam concluded that the Bence Jones protein in the urine could not be derived from the abnormal serum component but was formed *de novo* from the amino acids in the body. Nevertheless, the similarity of the abnormal serum and urine constituents on electrophoretic analysis may be very striking indeed, although their rates of migration often differ slightly [*47*].

It is of some significance that in the patients with multiple myeloma, excluding the abnormal myeloma-type of protein, the residual gamma globulin was subnormal in 76 per cent of the cases. (Fig. 16.) It is considered that in the more

pronounced cases this represents a true hypogammaglobulinemia not unlike that seen in patients with chronic lymphatic leukemia. Repeated infections, difficult to control, were a common occurrence in some of these patients. The demonstration by other investigators of a poor antibody response to antigenic stimuli in such cases [*53,54*] supports the view that there may be a deficiency of the normal (antibody) gamma globulin in some patients [*45,55,56*].

Other Diseases with Abnormal Protein Components. Although a narrow band or peak of abnormal protein, as demonstrated by electrophoretic examination, is highly characteristic of multiple myeloma, it is not diagnostic. Narrow bands of abnormal globulins of this type may be observed in rare instances of unexplained macroglobulinemia [*43,50*] or cryoglobulinemia [*57–59*], and in patients with a high content of macroglobulins, cryoglobulins or other abnormal proteins associated with malignancy, leukemias, lymphomas, certain "reticuloses," primary amyloid disease, collagen disease syndromes and even in one seemingly healthy donor [*40,50,51,58,60,61*]. The present study includes ten patients in whom electrophoretic patterns exhibited an abnormal protein constituent similar to that which may be found in multiple myeloma, but in whom the diagnosis of multiple myeloma could not be verified. Macroglobulinemia was not excluded in any of these patients since ultracentrifugal studies were not carried out.

Case I (SBH 47432). While under investigation in 1957 for steatorrhea with ascites and dependent edema, the first of these patients, a sixty-eight year old man, suddenly died of a pulmonary embolus. The hemoglobin was 10.1 gm. per cent; red blood cells, 3.9 million per cu. mm.; white blood cells, 9,400 per cu. mm.; erythrocyte sedimentation rate, 105 mm. in one hour (Westergren). Bone marrow examination before death showed erythrocytic hypoplasia and granulocytic hyperplasia with small foci of lymphocytes and lymphoblasts. There were no skeletal lesions on radiological examination. The electrophoretic pattern showed a typical myeloma-type of protein in the serum and urine, with the mobility of a gamma globulin. Postmortem examination disclosed primary amyloid disease. Because the marrow, liver, kidneys and lymph nodes showed a focal infiltration with small lymphocytes and a few plasma cells, with almost complete obliteration of the follicular structure in the lymph nodes and a tendency to invade the capsule, a diagnosis of malignant lymphoma was entertained.

Abnormal protein constituents have been described in primary amyloidosis by other authors [*51,60,61*]. Osserman [*51*] reported abnormal myeloma-type proteins in nine of ten patients with primary amyloidosis and suggested that they may be clinicopathologic variants of multiple myeloma. In his view the demonstration of the characteristic abnormal proteins in the serum or urine justified their inclusion within the spectrum of multiple myeloma. Ten patients with lymphoma were also included by this author as variants of multiple myeloma for this reason.

Case II (SBH 2626). A sixty-eight year old man was admitted to the hospital in 1956 with pneumonia, anemia and a high sedimentation rate. The hemoglobin was 8.9 gm. per cent; red blood cells, 3.0 million per cu. mm.; white blood cells, 6,400 per cu. mm.; erythrocyte sedimentation rate, 125 mm. in one hour (Westergren). A urinalysis showed 2-plus proteinuria. The result of the Bence Jones test was negative. After recovery from the pneumonia, electrophoretic examination demonstrated a typical abnormal component in the beta position in the serum, and a single abnormal band in the urine in the same position. Bone marrow aspirations at two sites were normocellular but contained scattered foci of small lymphocytes and a few plasma cells. No skeletal lesions were evident on radiological examination. A repeat biopsy of the bone marrow, following readmission to the hospital in 1958 for generalized weakness and pains in the shoulders, was unchanged. However a biopsy specimen of a nodule on an eyelid showed diffuse infiltration of the tissue with lymphocytes and some plasma cells, the pathological appearance suggesting a malignant lymphoma.

Case III (TGH E30664). A sixty-two year old man was admitted to the hospital in 1958 with an active duodenal ulcer, anemia and generalized weakness. A few rather firm, enlarged lymph nodes were felt in the left axilla, there was a grade 2 systolic murmur at the cardiac apex and several small hemorrhages were present in the fundus of the left eye. The hemoglobin was 5.5 gm. per cent; red blood cells, 1.8 million per cu. mm.; white blood cells, 2,500 per cu. mm.; normal differential count; platelets, 40,000 per cu. mm.; and erythrocyte sedimentation rate, 153 mm. in one hour (Westergren). Electrophoretic examination of the serum showed a myeloma-type protein in the gamma position. Biopsy specimens of bone marrow from several sites showed a hypoplastic marrow predominantly lymphocytic in character. A biopsy specimen of an axillary lymph node was compatible with a diagnosis of malignant lymphoma.

Case IV (SBH 67487). A forty-four year old RCAF Sergeant was admitted to hospital in 1957

with an upper gastrointestinal hemorrhage following a subtotal gastrectomy for duodenal ulcer. Rather abruptly over the next three months a clinical picture developed suggestive of a rapidly progressive scleroderma, terminating fatally. The hemoglobin was 11.8 gm. per cent; red blood cells, 4.0 million per cu. mm.; white blood cells, 5,600 per cu. mm.; erythrocyte sedimentation rate, 108 mm. in one hour (Westergren). The bone marrow was hypoplastic, with some increase in mature plasma cells, but there were no skeletal lesions on roentgenographic examination. The electrophoretic pattern showed a typical narrow band in the gamma position. At autopsy the diagnosis of scleroderma could not be confirmed with certainty but no other cause was found to explain the presence of the abnormal serum component.

Case v. Miss M. F., a sixty-three year old female missionary, was seen because of a rash over the butterfly region of her face and upper part of her chest, associated with general malaise and tachycardia. While the patient was receiving treatment with chloroquin the rash became more generalized, but was later brought under control with steroid therapy. The reaction to a L.E. test was negative. The serum protein pattern showed a typical myeloma-type protein between the beta and gamma globulins. It was concluded that this woman had a collagen disease, possibly systemic lupus erythematosus, with an unexplained abnormal protein constituent.

Case vi (SBH B8210). A fifty-eight year old man had had severe rheumatoid arthritis for fifteen years. During the last five years a clinical picture developed of Felty's syndrome with anemia, leukopenia, thrombocytopenia, splenomegaly, hepatomegaly and repeated infections. The hemoglobin was 10.8 gm. per cent; red blood cells, 3.9 million per cu. mm.; white blood cells, 1,200 per cu. mm.; and platelets, 130,000 per cu. mm. Numerous bone marrow aspirations over this period showed only myeloid hyperplasia with maturation arrest in the myeloid series. An abnormal band of protein was demonstrated electrophoretically both in the serum and in extracts of cellular marrow; this band was located between the beta and gamma fractions. Following splenectomy there was no change in the protein pattern although there was an excellent hematologic response.

Case vii (SBH R116817). A sixty-one year old man with Marie-Strümpell spondylitis was found on investigation to have a cold precipitate in his serum which redissolved on warming, appearing as an abnormal narrow band in the gamma globulin position. The hemoglobin was 11.2 gm. per cent; white blood cells, 7,300 per cu. mm.; erythrocyte sedimentation rate, 37 mm. in one hour (Westergren). This patient has had no symptoms referable to cryoglobulinemia.

Case viii (TGH E14469). A fifty-six year old man with cold hypersensitivity for five years and urticaria with purpura for two years was admitted to the hospital in 1958 with recent complaints of joint pain, epigastric distress, hepatomegaly and purpura over both legs. The hemoglobin was 9.4 gm. per cent; white blood cells, 9,300 per cu. mm.; erythrocyte sedimentation rate, 50 mm. in one hour (Westergren). Urinalysis showed a 2-plus proteinuria. A cryoglobulin was present in a concentration of 0.26 gm. per 100 ml. Electrophoretic examination demonstrated this as an abnormal narrow band in the gamma position, with a similar band in the urine. Bone marrow aspiration showed many large, foamy plasma cells, some of which were binucleate. A skeletal survey did not show any lesions of bone.

Case ix (TGH D79351). This forty-seven year old woman was admitted to the hospital in 1958 with generalized weakness and an anemia of unknown etiology. The liver and spleen were moderately enlarged. The hemoglobin was 7.0 gm. per cent; red blood cells, 2.4 million per cu. mm.; white blood cells, 4,000 per cu. mm.; platelets, 90,000 per cu. mm.; and erythrocyte sedimentation rate, 154 mm. in one hour (Westergren). Urinalysis showed a 2-plus proteinuria. Two bone marrow aspirations and one bone biopsy specimen all showed a hypoplastic marrow but with some increase in small lymphocytes. The reaction to the Sia test was strongly positive. Electrophoretic analysis revealed an abnormal narrow band in the serum and urine having the mobility of a gamma globulin. As there was no other explanation for the hypoplastic anemia and pancytopenia, it appears probable that the abnormal protein constituent represents a macroglobulin.

Case x. Mrs. P. R., a forty-eight year old woman, was examined because of extreme anxiety, spells of depression and generalized skeletal bone pains. The physical examination was within normal limits. The hemoglobin was 10.9 gm. per cent; white blood cells, 5,700 per cu. mm.; erythrocyte sedimentation rate, 70 mm. in one hour (Westergren). Electrophoretic analysis of the serum revealed an abnormal narrow band of protein in the gamma position. Bone marrow aspiration was normal, with a few mature plasma cells, but there were no radiological lesions on skeletal survey. A definite diagnosis was not made.

Cryoglobulinemia. Essential cryoglobulinemia is a rare disease [*57,59*]. One example has been reported from this Center, exhibiting an abnormal narrow band of protein in the gamma position which precipitated in the cold in concentrations up to 1.6 gm. per 100 ml. [*57*]. Three other patients with significant amounts of serum cryoglobulins, up to 0.3 gm. per 100 ml., have been observed. Two of these also had abnormal myeloma-type bands in the serum

electrophoretic strips. Brief summaries of their case histories are listed in the preceding section under Cases VII and VIII. The third patient presented with marked lymphedema of the face associated with a dermatitis. Biopsy of the skin lesion suggested Hodgkin's disease but this was never verified. A cryoglobulin was present in the serum but there was no abnormal band on electrophoretic analysis.

In attempts to reconstitute cryoglobulins after precipitation in the cold it has been found that the precipitate may trap small amounts of albumin and other globulin components, in spite of repeated washing. Henstell [*62*] has suggested that prothrombin and accelerator factors may be brought down as well.

Trace amounts of cryoglobulins have been encountered in a variety of other diseases but the significance of this observation is not known. Another patient with Marie-Strümpell spondylitis was found to have an abnormal fibrinogen in high concentration, which caused the plasma to form a solid gel on exposure to cold. This patient, however, did not show geling of the serum or an abnormal band in the serum electrophoretically.

Agammaglobulinemia and Hypogammaglobulinemia. Mention may be made of three young adults, two males and one female, with so-called agammaglobulinemia [*63–65*] associated with histories of repeated infections. (Table I, Fig. 18.) The gamma globulin values were reduced to levels of 0.06 to 0.17 gm. per 100 ml., but it is probable that the true values were even lower, in view of the known trailing of other protein fractions which are measured as well. Two patients with the acquired type have been considerably improved on a program of prolonged and continued administration of human gamma globulin over periods of two to three years. The third patient, who conformed to the congenital type (an eighteen year old male not included in the general group of rheumatoid arthritis), had suffered from juvenile rheumatoid arthritis (Still's disease) for about ten years, although this was relatively quiescent on the occasion of his last admission to hospital. Both the sheep cell agglutination and latex fixation tests were negative in this instance. He has also been started on a course of treatment with human gamma globulin.

As has already been stated, excluding the abnormal myeloma-type protein, a significant decrease in the normal gamma globulin component may be observed in a high proportion of patients with multiple myeloma. Significant reduction of the gamma globulin fraction may also be observed in most patients with the nephrotic syndrome resulting from glomerulonephritis, in a proportion of patients with chronic lymphatic leukemia, occasionally in lymphomas and in a few patients given prolonged therapy with corticosteroid hormones for various reasons. Among the more striking examples, the electrophoretic pattern in one patient with chronic lymphatic leukemia in whom the gamma globulin was very low (Fig. 13) was indistinguishable from that of agammaglobulinemia. A similar reduction of the gamma globulin has been reported in patients with malignant lymphoma [*42,66*], one example of which has been encountered in the present study. (Fig. 14b.) Finally, a comparable but less pronounced reduction of the gamma globulin was observed in one patient with multiple myeloma in the absence of any abnormal protein in the serum. (Fig. 17c.) In this instance, however, an abnormal myeloma-type protein was demonstrated in the urine. (Fig. 17d.)

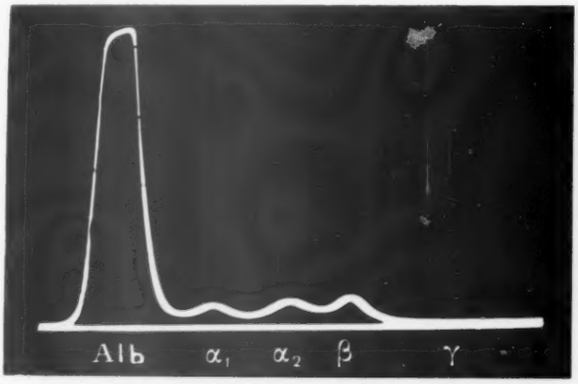


FIG. 18. Representative electrophoretic pattern of the serum proteins in a patient with congenital agammaglobulinemia.

SUMMARY

The results of electrophoretic determinations of the serum proteins in a group of 100 normal subjects and in subjects with a wide variety of disease are summarized. The observations indicate that the total quantity of the serum proteins and the concentration of the various globulin components in the normal subject remain fairly constant within a relatively narrow range. Determinations showing significant deviation from the normal values have not, in general, been consistent with continued good health. At

the same time it should be stressed that normal serum electrophoretic patterns may be observed in a proportion of most of the diseases which have been included in this study.

Hyperglobulinemia with hypergammaglobulinemia may be observed in a variety of disease states including rheumatoid arthritis and other "collagen diseases," chronic liver disease, chronic ulcerative colitis, sarcoidosis, certain infective states, various types of thrombocytopenic and non-thrombocytopenic purpura, cryoglobulinemias and macroglobulinemias, lymphomas, multiple myeloma, primary amyloid disease and in some obscure illnesses in which a definite diagnosis can not be made even after autopsy examination.

An increase in the gamma globulin over its whole breadth, such as commonly occurs in rheumatoid arthritis, systemic lupus erythematosus and related "collagen diseases," chronic liver disease and in a variety of other disease states, is not distinctive and appears to be of little diagnostic value other than that it may reflect a disturbance of the antibody-producing mechanism. The appearance of abnormal protein constituents, however, occurring in relatively narrow bands usually located somewhere in the region of the beta or gamma components, may be of distinct value in diagnosis. Such patterns were observed most commonly in multiple myeloma. Not infrequently a similar abnormal protein may be shown in the urine, and in the present instance was consistently demonstrated in multiple myeloma whenever there was an associated proteinuria. The demonstration of such abnormal bands by electrophoretic analysis is not, however, diagnostic of multiple myeloma since they were observed in a smaller proportion of other illnesses, including obscure diseases in which an accurate diagnosis could not be made either clinically or after postmortem examination. While it is a simple matter to determine whether or not cryoglobulins are present in such cases, the presence of macroglobulins can be verified only by ultracentrifugal study.

Examination of the serum proteins in patients with a clinical picture of the nephrotic syndrome may be helpful in differentiating nephrosis due to glomerulonephritis from systemic lupus erythematosus and other diseases associated with renal involvement, when other characteristic changes are lacking. Patients with the nephrotic syndrome resulting from glomerulonephritis showed a greatly increased alpha^2 fraction and reduced gamma globulin, in contrast to the relatively normal apha^2 fraction and normal gamma globulin observed in patients with the nephrotic syndrome due to systemic lupus erythematosus and other diseases with renal manifestations.

In patients with agammaglobulinemia and hypogammaglobulinemia due to various causes, electrophoretic analysis of the serum proteins is a simple and reliable method of demonstrating this deficiency.

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Seminar on Mycotic Infections

The Use of Amphotericin B in the Treatment of Coccidioidal Disease*

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COCCIDIOIDOMYCOSIS, also known as Valley or San Joaquin Fever, continues to be the most important of the fungus-produced diseases in the Western United States. The morbidity due to primary coccidioidal infection probably exceeds 35,000 cases per year. Endemic throughout Southern California, Southern Nevada, Arizona, Western Texas and the adjoining Mexican territory, it has been intensively studied by investigators within this area. Its growing importance at a national level can be attributed to the constant ebb and flow of our mobile American population through this scenic vacation land, and the assignment of non-immune personnel to military bases and air research centers within the contaminated zone. Progressive agricultural development and continuing reclamation projects within this same area have resulted in a growth of population exceeding that anywhere else in this country. In this respect, and in consideration of the public health significance of coccidioidomycosis among the resident population, Smith and his co-workers state, "It is immaterial whether infections occur at a rate of 25 per cent per year or 8 per cent per year; ultimate infection is inevitable [*1*]."

Primary coccidioidomycosis is only a mild infection in two-thirds of persons who are not sick enough to seek medical attention. The remaining third, who are more severely ill, seek help and usually have acute pulmonary lesions demonstrable on the chest roentgenogram. It is estimated that 5 per cent of patients recovering from the initial infection are left with residual pulmonary changes, including cavitation, solid pulmonary foci (coccidioidoma), areas of fibrotic scarring, localized bronchiectasis and calcified lymph nodes and parenchymal deposits. Failure of the primary infection to focalize permits dissemination of the infectious agent (C. immitis) to occur, resulting in a catastrophic illness, with a 60 per cent mortality. Fortunately, this untoward development remains infrequent (less than 0.5 per cent of cases) but becomes a greater threat in dark-skinned patients, particularly in the Filipino, Negro and Mexican.

No other fungus disease has had such intensive study [*2,3*], and this has led to an accurate portrayal of the protean aspects of coccidioidomycosis [*4*], including its ecology [*5–7*], its dimorphic form of growth in the soil and in man, epidemiology, serologic evaluation [*8*] and diagnostic criteria. The gross and microscopic pathology of the disease in the primary and disseminating phases has been carefully described and correlated with the roentgenographic findings [*9–11*]. Such understanding of the natural course of a mycotic disease is a prerequisite to the application of effective therapy, whether medical or surgical. From the surgical aspect [*12*], one is chiefly confronted with residual pulmonary changes, in particular the cavity and the coccidioidoma, left behind by primary coccidioidomycosis. In dissemination, treatment is chiefly medical and of new importance with the advent of amphotericin B [*13*]. Along with the use of this antibiotic in disseminating disease, fully effective therapy also requires the application of such well established surgical principles as drainage of abscesses, excision of sinuses, removal of infected bone, cauterization of metastatic lesions of the skin, and even amputation, when indicated [*14*]. This same principle also applies to the drainage of infected spinal and pleural fluid by frequent lumbar taps or thoracenteses. Supportive treatment, for the sick patient with severe primary or disseminating coccidioidomycosis, should include hospital and nursing care, maintenance of bodily nutrition with a high protein and vitamin intake, and whole blood transfusions as

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TABLE I
INDICATIONS FOR THERAPY WITH AMPHOTERICIN B IN COCCIDIOIDAL DISEASE

1. Persistent fever, prostration, elevated blood sedimentation rate, with considerable pulmonary involvement and hilar adenopathy
2. Unstable serology, i.e.:
   (1) Rising titer of complement fixation above 1:64 dilution
   (2) Persistent precipitins
   (3) Incomplete complement fixation
3. Evidence of spread from primary pulmonary focus:
   (1) Invasion by C. immitis of lymphatic, cutaneous, skeletal, cardiac, genitourinary, and meningeal systems, or pleuro-peritoneal space
4. Weak or negative skin reaction to coccidioidin
5. Member of susceptible race; i.e., Negro, Filipino, Mexican
6. As surgical coverage, given three to four weeks before operation in:
   (1) Removal of large pulmonary cavities or destroyed areas of lung
   (2) Other excisional or drainage procedures including removal of infected bone, gonads, lymph nodes, abscesses and sinus tracts
   (3) In conjunction with high-frequency electrical coagulation of granulomatous skin lesions and superficial abscesses
7. In certain metabolic situations:
   (1) Pregnancy
   (2) Diabetes mellitus

indicated. Physical rest should be assured by appropriate medication for symptomatic relief.

Physicians dealing with coccidioidal disease have felt a great need for an effective fungistatic or fungicidal preparation that could be used for (1) the control of severe primary coccidioidomycosis, (2) the arrest of dissemination, including coccidioidal meningitis, (3) the healing of peripheral granulomas and abscesses, (4) surgical coverage to prevent the occasional severe complications that follow surgical manipulation, and (5) protection of the pregnant patient who has contracted primary coccidioidal disease.

Many compounds and antibiotics have been recommended, but adequate proof of their effectiveness has been lacking, and they have been ultimately discarded. The isolation and availability of amphotericin B, reported by Gold in 1956 [*15*] and Vandeputte et al. [*16*], and its effectiveness against C. immitis in animals, as described by Sternberg [*17*], Steinberg [*18*], and Halde [*19*] and their associates, soon led to its clinical use as reported by Littman [*20,21*], Seabury [*22*], Colwell [*23*], Newcomer [*24*], Utz [*25*] and Klapper [*26*] and their co-workers.

Our own observations with this antibiotic began in 1956 and indicate that it is effective, when properly used, in severe primary coccidioidal disease, in infection threatening to disseminate, and in disseminated disease, including coccidioidal meningitis. Our experience would also support the value of amphotericin B in the healing of peripheral skin granulomas, abscesses and secondary sinuses, and lymphadenitis. As a "covering" drug it deserves consideration prior to surgical procedures involving the manipulation and removal of any lesion harboring viable C. immitis. And finally, on the basis of reported instances [*29,30*] of a tendency for acute primary coccidioidomycosis to disseminate in pregnant women, it would appear to be of prophylactic value in this respect.

It remains necessary, in using this antibiotic, to employ a dosage just as intensive in the treatment of severe primary coccidioidomycosis as in disseminating disease, if one is to achieve serologic evidence of adequate response, as indicated by a lowering of the titer of complement fixation. Such serologic evaluation would provide the ultimate criterion for the true effectiveness of amphotericin B in coccidioidal disease, since the test is of proved specificity and prognostic accuracy [*31*].

Amphotericin B must be given either intravenously or intrathecally, and is not a simple antibiotic to use. There is little evidence for any value in the oral or intramuscular administration of this antibiotic in treating coccidioidal disease. Seabury states that its use should not be casual [*22*], and will require some ingenuity in suppression of side reactions. Definite indications for its use have been formulated. (Table I.) Once the patient has been committed to this form of therapy it must be given in sufficient dosage and often enough to maintain an effective blood serum level of at least 0.5 to 1.0 μg./ml. Such a level should be sustained long enough to gain, when possible, a definite decrease in the titer of complement fixation. (Table II.) This ultimate and desired response is usually preceded by improvement in both the clinical condition of the patient and in the changes on x-ray films. Justification for prolonged treatment resulting in such desirable serologic reversal lies in the prevention of relapse. This may require three to four months of administration, without undue interruption. If relapse does occur, one should not hesitate to repeat the course of therapy (see Case 2). However, relapse will not usually occur in patients who show good serologic response to therapy.

TABLE II

RESULTS OF AMPHOTERICIN B THERAPY IN SEVERE AND DISSEMINATED COCCIDIOIDAL DISEASE (TEN CASES)

Case No.	Type of Disease	Serological Titer B.T.*	Last Serological Titer	Observation A.T.* (mo.)	Results
1	Severe pulmonary	4+ 1:512	3+ 1:64	18	Complete recovery
2	Severe pulmonary	4+ 1:512	3+ 1:64	8	Complete recovery from relapse
7	Severe pulmonary	2+ 1:128	2+ 1:32	4	Well and working
4	Severe pulmonary	2+ 1:256	3+ 1:8	14	Well and teaching
6	Massive pleuritic effusion and hilar adenopathy	4+ 1:256	Entirely negative	6	Well, at school
3	Severe pulmonary, cervical adenitis	3/12/57 2+ 1:1024	7/31/57 4+ 1:256	26	Living in Philippines reported by letter 1/59; working and well
8	Massive pleuritic effusion and hilar adenopathy	1+ 1:256	2+ 1:8	3	Well and working
5	Severe pulmonary, skin and skeletal	5/21/58 4+ 1:256	3/18/59 2+ 1:128	9	Housework, pregnant, apparently well
9	Severe pulmonary, marked hilar adenopathy	4+ 1:64	2+ 1:32	2	Convalescing well
19	Five deep lumbar and inguinal abscesses positive for C. immitis	2+ 1:256	4+ 1:64	6	Complete healing second week after completion of intravenous treatment; well and working

* B.T. = Before treatment started. A.T. = After treatment concluded.

The usual intravenous dosage, based on body weight, is a minimum of 1 mg./kg. for the adult, and from 1.25 to 1.50 mg./kg. for the child or infant. One-fifth of this dosage is given initially, diluted with 500 to 750 cc. of 5 per cent dextrose in water. By the end of the first week the full dosage can usually be attained. Recently, we have come to give amphotericin B intravenously every twenty-four hours, and have recognized, along with this, the importance of careful intravenous technic. This requires small needles of 22 to 24 gauge, starting with distal venous tributaries, and avoiding perivascular infiltration by the amphotericin B solution. Such measures are mandatory in the prevention of complicating phlebitis which can interfere with the necessary length of treatment required for control of severe coccidioidal infection. In addition to using well diluted and freshly prepared solutions, the inclusion of 10 to 20 mg. of heparin sodium may minimize phlebitis. Antihistamines, such as diphenhydramine hydrochloride, can be added to the intravenous solution to alleviate the initial febrile reactions. Patient cooperation should be obtained by careful preliminary explanation; such rapport is essential to successful completion of therapy. (Table III.) Our technic of intravenous administration is described in Figure 1.

In our experience, the toxic effects and side reactions have been controllable and are not permanent. This includes elevation of the blood urea nitrogen (which responds to a slight temporary lowering of the dosage), following which we have seen no evidence of renal damage. Lowering of the hemoglobin and red cell values would indicate either bone marrow depression or evidence of hemolysis. This will require transfusion, and iron and vitamin B_{12} therapy. Anorexia, nausea and vomiting can be minimized by the addition of 100 mg. of pyridoxine hydrochloride to the intravenous solution. Such gastrointestinal symptoms may also respond to trifluprom azine hydrochloride (vesprin, Squibb) 10 to 15 mg., given intramuscularly thirty minutes prior to treatment, or hydroxyzine pamoate (vistaril, Pfizer), given beforehand in the same dosage and manner. Chills and febrile reactions, which are most apt to occur during the early period of intravenous therapy, are also minimized by maintenance of body temperature (electric blankets, hot water bottles), slow

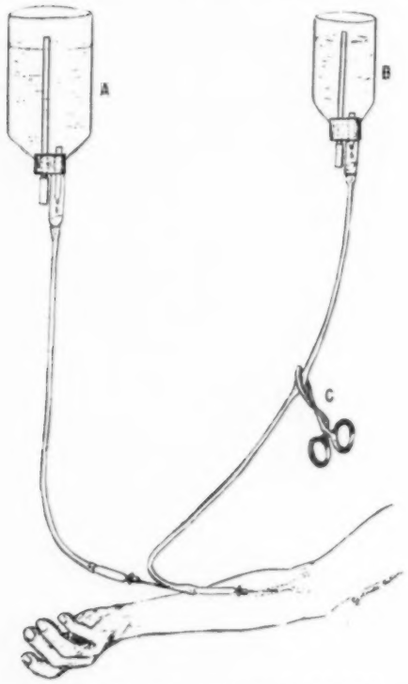


FIG. 1. A method for the control of phlebitis and side effects during intravenous administration of amphotericin B. A small needle (gauge 22 or 23) is used and introduced into a peripheral vein with a 2 cc. syringe (a special scalp vein set-up is used in small children).* This is connected to bottle B containing 150 cc. of 5 per cent dextrose in water, plus any desired additives such as: (1) pyridoxine hydrochloride, 100 mg. (control of anorexia, emesis). (2) vitamin B_{12}, 500 μg. (bone marrow stimulation). (3) ascorbic acid, 500 mg. Bottle A containing 500 to 750 cc. of 5 per cent dextrose in water, plus the desired dose of amphotericin B, is connected by a 20 or 21 gauge needle into the terminal portion of the bottle B tubing. (1) Average intravenous dose amphotericin B (adults) = 1 mg./kg. (2) Average intravenous dose amphotericin B (children) = 1.5 mg./kg. The following additives are included in this solution of amphotericin B in bottle A: (1) Diphenhydramine hydrochloride, 10 to 30 mg. (Chlorprophenpyridamine maleate, 10 mg., may be used instead.) (2) Heparin sodium, 10 to 30 mg. Chills during and following the intravenous administration of amphotericin B are minimized by: (1) Extra blanket (electric) or hot water bottles. (2) Warming intravenous solutions by binding lower portion of tubing to hot water bottle with a towel. (3) By fifteen minute "cut-off" technic. Clamp is changed by the nurse from bottle B tubing to bottle A tubing every fifteen minutes for a period of two to three minutes. The patient may do this at any time himself by changing the clamp, which is left within reach, and whenever he begins to feel cold. This procedure also minimizes phlebitis by washing out the vein periodically. If a chill develops, this method permits continuation of intravenous administration, giving only bottle A (5 per cent dextrose in water) slowly, until the chill subsides, and then restarting amphotericin B by changing the clamp. Premedication, usually necessary in the early course of intravenous treatment, and given thirty minutes beforehand, may include 5 to 10 gr. acetylsalicylic acid (may be repeated in two hours) and/or 25 to 50 mg. of diphenhydramine hydrochloride (Benadryl).

* This is available from Cutter Laboratories, Berkeley, California.

TABLE III
USE OF AMPHOTERICIN B (INTRAVENOUSLY) IN COCCIDIOIDAL DISEASE

1. A definite need established, then skilled and dedicated use
2. Commitment to treatment involves:
   - (1) Rapport with patient insuring full cooperation
   - (2) Intravenous therapy started with low dosage and symptomatic control of side effects
   - (3) Given intravenously daily (may have Sundays off) for *minimum* period of two months
   - (4) Careful use of veins, using small needles and beginning peripherally
   - (5) Correct preparation of solutions and proper technic in administration
   - (6) Adequate dosage based on body weight and by determination of biweekly amphotericin B serum levels: Adults, 1 mg./kg.; children, 1.5 mg./kg.
   - (7) Protection of patient by hematologic and biochemical studies:
     - (1) Biweekly blood count, blood urea nitrogen, occasional creatinine, phenolsulfonphthalein, cephalin flocculation and bromsulphalein tests
       - (a) Temporary lowering of dosage with marked elevation in blood urea nitrogen
       - (b) Transfusion for secondary anemia
   - (8) Length of treatment guided by serial x-rays, serologic and bacteriologic studies, the response of disseminated foci and maintenance of clinical improvement
   - (9) In general, sufficient therapy has been given when titers show definite and sustained decrease
   - (10) Treatment of severe primary infection requires as full scale treatment as that given for disseminating disease
   - (11) Antibiotic therapy (i.e., amphotericin B) must always be used with indicated and definitive surgical treatment: (1) To eradicate distant foci by allied surgical drainage, débridement, excision, cauterization

administration over a two-to-four-hour period, and the fifteen minute "cut-off" technic (Fig. 1), together with salicylates given before and during treatment. In the first week or two of therapy, the following is usually given thirty minutes before the intravenous administration of amphotericin B: (1) acetylsalicylic acid 5 to 10 gr., and (2) diphenhydramine hydrochloride (Benadryl,® Parke-Davis), 25 to 50 mg. orally. The dosage of salicylate may be repeated in two hours. It has been our practice to have intra-

TABLE IV
TREATMENT OF COCCIDIOIDAL MENINGITIS WITH AMPHOTERICIN B

1. Intravenous and intrathecal therapy given simultaneously, i.e.:
   (1) Daily intravenous therapy
   (2) Intrathecal injection every 24 to 48 hours
2. Spinal fluid pressures kept within normal range by removal of *sufficient* cerebral spinal fluid every 24 to 48 hours:
   (1) Prevents block and hydrocephalus
   (2) Principle of surgical drainage removes exudate, infective agent, etc.
   (3) May increase passage of amphotericin B from blood stream through the meningeal barrier
3. Good technic requires:
   (1) Rigid bacteriologic and aseptic precautions
   (2) Correctly performed lumbar puncture, with variation of sites
   (3) Intrathecal injection of freshly prepared and *well diluted* aqueous solution of amphotericin B, mixed with spinal fluid and injected slowly, not exceeding 0.7 mg. per injection
4. Length of treatment guided by studies of cerebral spinal fluid:
   (1) Serology, determinations
   (2) Cell count
   (3) Cultures
   (4) Protein and glucose
   (5) Manometric pressures

venous solutions freshly prepared and given only by the physician, who uses careful aseptic technics because of the ineffectiveness of amphotericin B against bacteriologic contamination of the solution.

In dealing with coccidioidal meningitis the appreciable impermeability of the meningeal barrier to amphotericin B presents a challenge. In addition, the meningeal membranes seem somewhat intolerant to higher concentrations of amphotericin B produced by direct instillation. A high blood serum level of amphotericin B will not in itself lead to increase in the drug level in the cerebrospinal fluid. Coccidioidal meningitis, being a surface type of pathologic infection, and rarely associated with deeper cerebral abscesses, results in rapid proliferation of C. immitis within the cerebrospinal fluid and the meningeal layers. The present therapeutic regimen (Table IV) therefore provides a weak concentration of amphotericin B within the cerebrospinal fluid, and a higher level in the blood serum. Repeated drainage of infected spinal fluid not only removes the infectious agent but also lowers the pressures within the subarachnoid space and, by lowering the cerebrospinal fluid proteins, tends to prevent fibrin deposit and blocking of the cerebrospinal fluid circulation and secondary hydrocephalus. Such a plan of therapy has resulted in complete control of four cases of coccidioidal meningitis, and arrest or clinical improvement in two other cases.

Despite the meningeal barrier to passage of any considerable amount of amphotericin B from the serum to the spinal fluid, adequate therapy for coccidioidal meningitis requires concomitant intravenous and intrathecal administration. The former should be given on a twenty-four-hour basis (six days a week), and the latter every forty-eight hours. Intrathecal administration may be even more frequent at first to reach the desired dosage quickly, and then retarded toward the end of therapy to seventy-two-hour intervals. By this method we have been able to demonstrate amphotericin B levels in cerebrospinal fluid of from 0.5 to 1.0 μg./ml., as long as twenty-four hours after intrathecal instillation. This could in part be due to the "timing" of intrathecal administration and spinal fluid drainage just prior to intravenous administration of amphotericin B. By not exceeding a dose of 0.7 mg. at a time, and using sufficient dilution in sterile distilled water, we have avoided arachnoiditis in the intrathecal treatment of five of our six cases of coccidioidal meningitis. Occasionally, we have included, in a separate syringe, a preliminary injection of hydrocortisone sodium succinate, as suggested by Seabury [*22*]. In Case 4, arachnoiditis developed after six months of intrathecal therapy, and symptomatic relief of pain in the back, seat and legs was obtained by intramuscular injection of 1 cc. of corticotropin (repository) in 15 per cent gelatin (Acthar gel). In intrathecal administration, as in intravenous administration, careful technic is necessary, including variation of the sites of carefully performed lumbar punctures from the first to the fourth lumbar interspaces. Sufficient cerebrospinal fluid is withdrawn each time (10 to 20 cc.) to lower the manometric pressures to normal, and preceding the administration of amphotericin B. This itself results in relief of headache or neckache, and is also believed to enhance the passage of the amphotericin B molecule, to a limited extent, from the blood serum through the meningeal barrier into the cerebrospinal fluid. Occasional discomfort

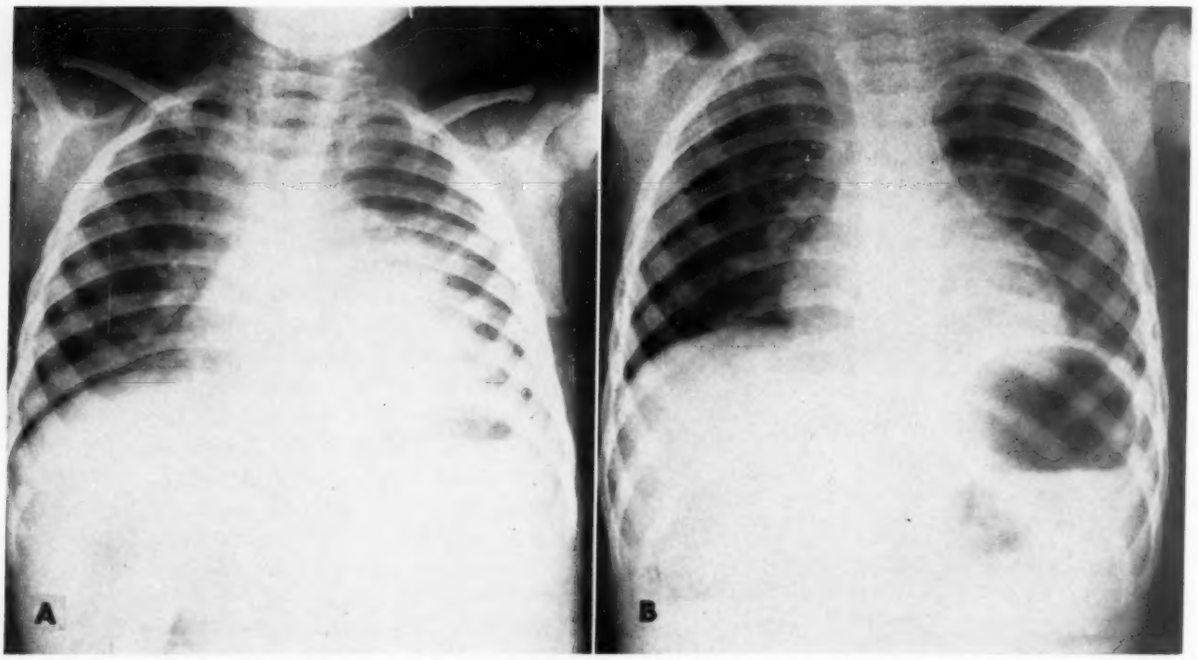


FIG. 2. Case 1. A, before treatment. B, after completion of seventy-two days of intravenous amphotericin B therapy.

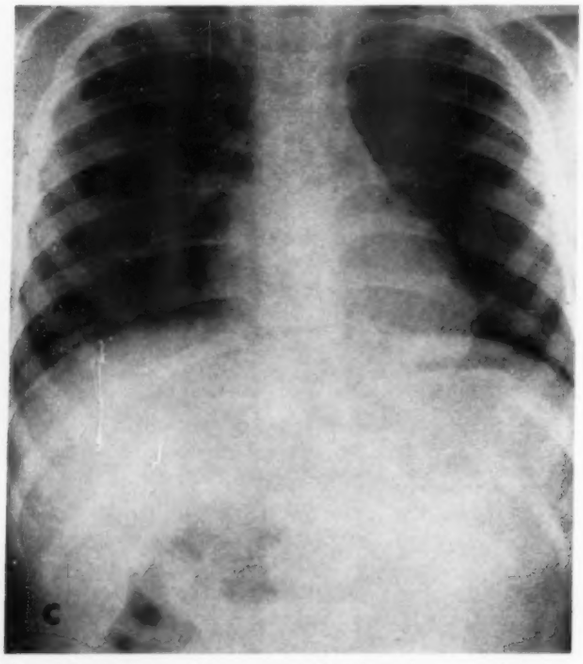


FIG. 2C. Case 1, eighteen months after therapy, showing complete clearing of pulmonary involvement.

following instillation of amphotericin B, such as pain in the legs or back, can be controlled by elevating the foot of the bed approximately 10 inches for one hour after administration.

Our conclusions are based on a cumulative experience with all phases of coccidioidal disease as previously reported [*27,28*], and intensive application of amphotericin B therapy to a group of twenty-two selected cases.

Nine cases were selected because of severity of the coccidioidal infection, racial susceptibility and variation in age.

CASE 1. Alf. S. (twin of Alb. S., Case 2), Negro male aged twenty-two months, was acutely ill when admitted, with a temperature of 102.4°F. A chest roentgenogram revealed pneumonitis in the lower lobe of the left lung, mottled densities in the lower lobe of the right lung and bilateral hilar adenopathy. (Fig. 2A.) A coccidioidin skin test was 2 plus (1:100), and complement fixation titer was 2 plus (1:16). Amphotericin B given orally in 1 to 2 gm. daily dosage for 126 days for a total dosage of 185 gm. was ineffective; the pulmonary infiltrations persisted and the complement fixation rose to 4 plus (1:256). Amphotericin B was then administered intravenously in a dosage of 1.5 mg./kg. every forty-eight hours over a period of seventy-two days for a total dosage of 0.64 gm. Blood levels of 0.5 to 1.0 μg./ml. were maintained. The blood urea nitrogen levels varied from 12 to 84 mg. per cent, returning to normal (14 mg. per cent) following treatment. The chest films showed improvement (Fig. 2B); the complement fixation titer was 4 plus (1:128) after three months. Twenty months after treatment the child was in excellent health; the chest films were clear (Fig. 2C); and the complement fixation was 3 plus (1:64).

Comment: This case is classified as threatened dissemination of coccidioidomycotic infection. Oral administration of amphotericin B was ineffective but a good clinical and serologic response was obtained by intravenous administration of the drug.

CASE 2. Alb. S. (twin of Alf. S., Case 1), Negro male aged twenty-two months, was acutely ill on admission with temperature of 102°F. A chest roentgenogram disclosed pneumonitis in the upper and lower lobes of the right lung with secondary hilar adenopathy. A coccidioidin skin test was 1 plus (1:100), and the complement fixation titer was 4 plus (1:512). Amphotericin B was given orally in 1 to 2 gm. daily dosage for 125 days for a total dosage of 187 gm. This was ineffective, with persistent high titer of complement fixation, and continued pulmonary involvement. Therefore, therapy with amphotericin B, administered intravenously, was started in a dosage of 1.5 to 1.7 mg./kg. every forty-eight hours over a period of ninety-one days for a total dosage of 0.95 gm. Blood levels of 0.6 to 3.0 μg./ml. were maintained. The blood urea nitrogen varied from 12 to 48 mg. per cent, returning to normal following treatment. Clinical and x-ray improvement followed but the titer of complement fixation remained at 4 plus (1:128). Ten months later clinical and roentgenographic relapse occurred, with persistent complement fixation of 4 plus (1:128) and reactivation of the pulmonary process as noted on the x-ray. A second course of amphotericin B was given in a dosage of 1.5 to 1.7 mg./kg. for a period of 118 days. Blood levels varied from 0.75 to 1.50 μg./ml. (these were determinations made forty-eight hours after intravenous administration). The blood urea nitrogen level rose to 102 mg. per cent but returned to 16 mg. per cent following treatment. The second period of intravenous treatment was followed by both x-ray and clinical improvement, and the complement fixation titer finally stabilized at a level of 3 plus (1:64). The patient remains well with no evidence of pulmonary changes nine months after treatment.

Comment: This case, also classified as impending dissemination of coccidioidal infection (the twin of Alf. S., Case 1), again demonstrates the superiority of intravenous administration of amphotericin B. Of great importance is the control of relapse by this antibiotic, which would indicate the inability of C. immitis to develop resistance to amphotericin B. This infant tolerated considerable dosage, given over a total period of 209 days, without any evidence of permanent toxicity. Recovery resulted, with stabilization of the titer of complement fixation at 3 plus (1:64) nine months after completion of therapy. In these two cases a simultaneous infection occurred, but with interesting differences in the respective resistance of the twins against coccidioidomycosis.

CASE 3. T. G., forty-eight year old Filipino man, was admitted acutely ill with a temperature of 103°F. and roentgenographic findings of consolidation in the upper lobe of the right lung and bronchopneumonic infiltrate in the lower and middle lobes of the right lung. Hilar adenopathy was present, followed by cervical adenopathy. Cultures from a draining cervical lymph node and a bronchial wash were positive for C. immitis. Eighty-eight intravenous injections of 250 mg. each of aminostilbamidine were ineffective and the complement fixation was 4 plus (1:256). Orally administered amphotericin B in a dosage of 4 gm. was given daily for eighty-four days for a total of 336 gm., but the complement fixation rose to 2 plus (1:1024). Amphotericin B was given intravenously daily for a short period in a dosage of 15 to 60 mg. for a total dosage of 0.36 gm. The blood urea nitrogen levels varied from 9 to 23 mg. per cent. The complement fixation fell to 4 plus (1:256) and stabilized at that point. The patient returned to the Philippine Islands and reported by letter twenty-one months later that he was working and in good health. An x-ray film revealed only minimal residual fibrosis in the upper right lung.

Comment: This case was classified as disseminating coccidioidomycosis. There was no response to the administration of either intravenous aminostilbamidine or oral amphotericin B but intravenous administration of amphotericin B resulted in recession of the complement fixation titer five weeks after beginning treatment, and was associated with marked clearing of the lungs. Although, immediately following therapy, the complement fixation titer remained at a 1:256 dilution, the patient is well twenty-one months after receiving amphotericin B.

CASE 4. C. F., a fifty-five year old Caucasian man, was admitted with a history of two and a half months of fever and cough, and roentgenographic findings of pneumonitis involving the lower lobe of the right lung with secondary hilar adenopathy. (Fig. 3A.) A coccidioidin skin test was 2 plus (1:100) and complement fixation 2 plus (1:256). Amphotericin B was given intravenously in a dosage of 40 to 60 mg. every forty-eight hours over a period of fifty-eight days for a total dosage of 1.42 gm. Blood level determinations made forty-eight hours after administration varied from 0.6 to 1.5 μg./ml. The blood urea nitrogen varied from 10.5 mg. per cent to a high of 46 mg. per cent. After therapy the complement fixation titer fell to 1 plus (1:64) and was accompanied by partial

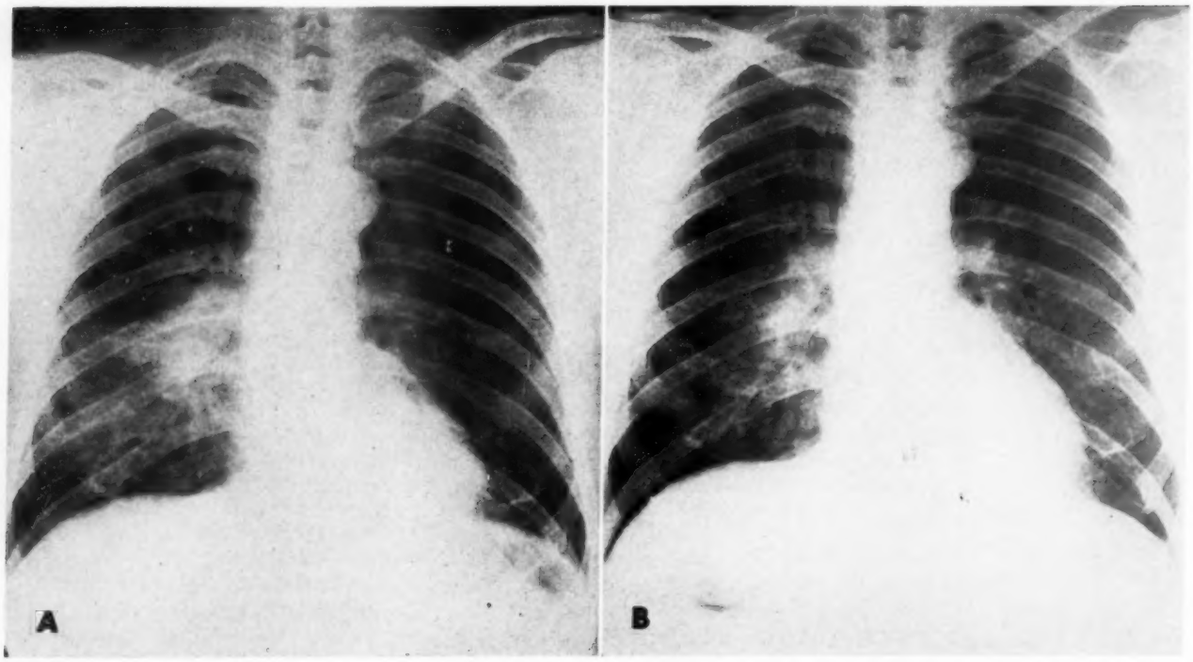


FIG. 3. Case 4. A, before treatment. B, six weeks after completion of two months intravenous amphotericin B therapy showing clearing of pneumonitis and decreasing hilar adenopathy.

clearing as demonstrated on the x-ray film. (Fig. 3B.) The patient has returned to full time teaching and remains well fourteen months after therapy. There are no residual changes evident on roentgenograms and the complement fixation is reduced to a titer of 3 plus (1:8).

Comment: This case was considered to represent impending dissemination. Persistent fever, pneumonitis and hilar adenopathy, together with a rapidly increasing titer of complement fixation, indicated the need for the intravenous administration of amphotericin B, which reduced the complement fixation titer five weeks after beginning treatment. He has remained well and working fourteen months after completion of therapy.

CASE 5. R. G., a thirty-six year old Mexican housewife, was admitted acutely ill with multiple granulomatous abscesses and draining sinuses of four years' duration, which were distributed over the anterior chest, breasts and axillae. Chest roentgenograms revealed miliary pulmonary infiltrate and an x-ray film of the pelvis disclosed an osteolytic lesion of the lower ramus of the left ischium. Cultures from the skin sinuses were positive for C. immitis. The patient was in the eighth month of pregnancy. A coccidicidin skin test was 2 plus (1:100), complement fixation was 4 plus (1:128). The intravenous administration of amphotericin B was started and a dosage of 50 to 70 mg. was given every forty-eight hours over a period of 167 days. The total dosage was 6.92 gm. The blood serum level varied from 0.5 to 3.0 μg./ml. at forty-eight-hour determinations. The blood urea nitrogen varied from 8 mg. per cent to a high level of 65 mg. per cent, returning to 12 mg. per cent following treatment. One month after the start of treatment the patient was delivered of healthy twins. Following delivery the lower ramus of the left ischium was resected. There was complete clearing as shown on the roentgenograms, accompanied by healing of the skin lesions. Nine months after therapy the patient remained well and the complement fixation had been reduced to 2 plus (1:128). She is now in the seventh month of her fourth pregnancy.

Comment: This case represents disseminated coccidioidomycosis, with miliary pulmonary involvement developing during pregnancy. Intensive therapy with intravenously administered amphotericin B, combined with surgical eradication of the osteolytic disease, protected the mother through a normal delivery of twins. There was also marked improvement of the extensive granulomatous skin lesions. She remains well nine months after therapy, even though she is again pregnant. The titer of complement fixation is 2 plus (1:128).

CASE 6. E. T. P., a ten year old male Indian, was admitted acutely ill with a temperature of 104°F.

Chest roentgenograms revealed extensive pleuritic effusion obscuring the left lower lung field. A coccidioidin skin test was reported negative (1:100), and when repeated, one month later, remained negative. Complement fixation was 4 plus (1:256). The intravenous administration of amphotericin B was started and given every twenty-four or forty-eight hours in a dosage of 40 to 50 mg. for ninety-nine days for a total dosage of 3.1 gm. The serum levels varied from 0.6 to 1.5 μg./ml. based on determinations made twenty-four hours after administration. The blood urea nitrogen varied from 13 to 24 mg. per cent, returning to 13 mg. per cent after treatment. Ten days after starting treatment the coccidioidin skin test became positive (1 plus, 1:100). Following treatment the complement fixation receded to 2 plus (1:128). The pleuritic effusion, much of which had been aspirated, was no longer present. Six months after therapy there were no residual changes noted on the x-ray films and the patient was well and attending school. The complement fixation had been reduced to 3 plus (1:32).

Comments: Poor sensitivity to coccidioidin in a ten year old Indian boy, with extensive pleuritic effusion and lung root lymphadenopathy, together with a high titer of complement fixation and a prolonged febrile state, indicated impending dissemination. The titer remained high one month after the start of intravenously administered amphotericin B, but ten weeks later it showed a definite fall, which continued. The child returned to school and remained well six months after discontinuation of therapy, and with a stabilized titer of 3 plus (1:32).

Case 7. T. T., a fifty-four year old Filipino man, was admitted moderately ill with persistent cough and with temperatures of 101.2°F. Roentgenographic examination disclosed consolidation of the lower lobe of the left lung with secondary hilar adenopathy. The coccidioidin skin test was 1 plus (1:100), complement fixation 2 plus (1:128). A course of intravenously administered amphotericin B in a dosage of approximately 1 mg./kg. was given every twenty-four to forty-eight hours over a period of eighty-one days for a total dosage of 3.32 gm. The amphotericin serum level varied from 0.6 to 6.0 μg./ml. taken twenty-four hours after administration. The blood urea nitrogen rose from 13 to 96 mg. per cent, and after treatment returned to 29 mg. per cent. The changes noted on the roentgenogram cleared and complement fixation fell to 1 plus (1:64) three months after treatment. Four months after therapy the patient remains well and has returned to field work. The chest roentgenogram discloses no residual pulmonary disease, and the complement fixation has fallen to 2 plus (1:32).

Comments: This patient was threatened with disseminating disease, heralded by a rising titer of complement fixation and persistent precipitins, and considerable pulmonary disease with secondary hilar adenopathy. There was good serologic response to intravenously administered amphotericin B within two months after beginning therapy, and this was accompanied by clearing of the lungs.

Case 8. P. B., a sixty-one year old Filipino man was admitted acutely ill with a four weeks' history of cough, chest pain, and fever with temperatures to 102.4°F. A chest roentgenogram revealed pleural effusion obscuring the right lung field. Aspiration of 1,400 cc. of thin serous fluid disclosed underlying hilar adenopathy and elevation of the right hemidiaphragm. A coccidioidin skin test (1:100) was doubtful, complement fixation was 2 plus (1:128), precipitin test 3 plus (1:10). Amphotericin B was given intravenously every twenty-four hours in a dosage of 1 mg./kg. for fifty-six days for a total dosage of 3.21 gm. Amphotericin B serum levels varied from 1.6 μg. to 6.0 μg./ml. based on determinations taken twenty-four hours after administration. The blood urea nitrogen varied from 15.5 mg. per cent to a high of 73 mg. per cent, later dropping to 47 mg. per cent. One month after starting amphotericin B the coccidioidin skin test became positive, 3 plus (1:10). There was no return of the pleural effusion, the adenopathy decreased slowly, and the complement fixation fell to 1 plus (1:16). Three months after therapy the patient remained well and returned to field work; roentgenograms have revealed no residual pulmonary changes. The complement fixation titer has fallen to 2 plus (1:8).

Comments: Impending dissemination of coccidioidal infection threatened this patient with extensive pleuritic effusion and a rather low sensitivity to coccidioidin. A prompt reversal of the rapidly rising titer of complement fixation and clearing of precipitins occurred two weeks after beginning therapy with intravenously administered amphotericin B. The lung root adenopathy tended to persist. He was able to return to field work ten weeks after beginning therapy, and has remained well for three months after discontinuation of treatment. The titer has receded to a low level of 2 plus (1:8), and there are no residual pulmonary changes.

Case 9. S. P., a four year old Negro girl, was acutely ill on admission, with a five weeks' history of respiratory infection and temperature of 104°F. The chest roentgenogram disclosed pneumonitis in the upper lobe of the right lung, and secondary hilar

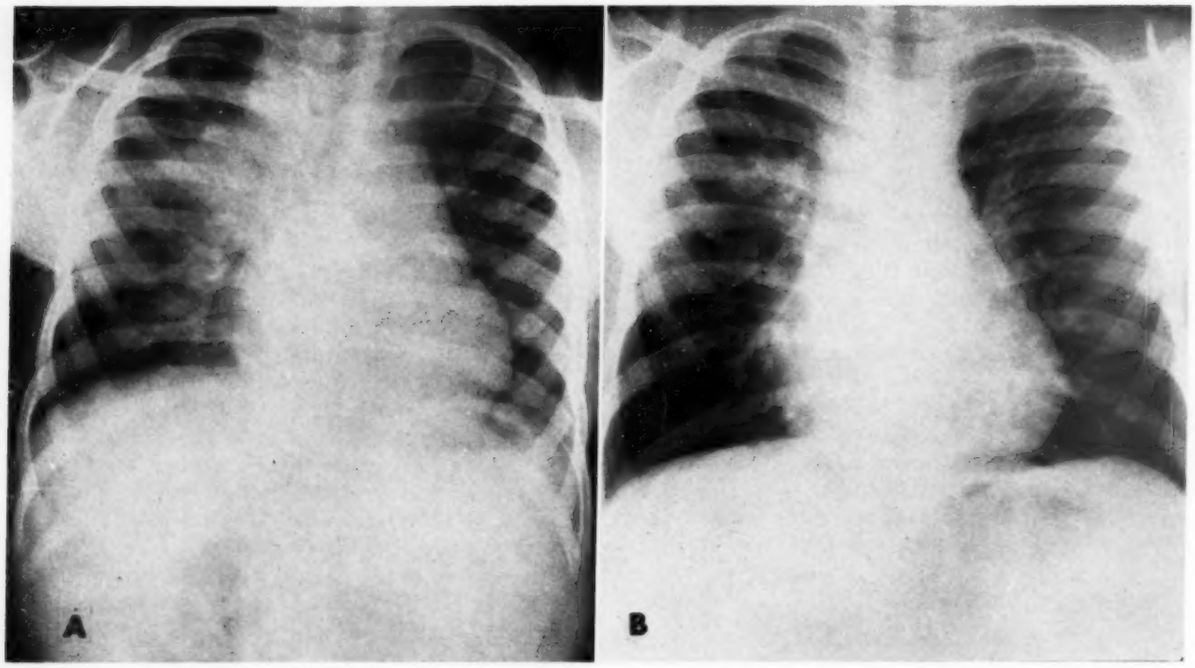


FIG. 4. Case 9. A, before treatment. B, three weeks after completion of eleven weeks of intravenous amphotericin B therapy showing considerable clearing and recession of adenopathy.

and paratracheal lymphadenopathy. (Fig. 4A.) A coccidioidin skin test was 1 plus (1:100). Complement fixation showed a rising trend and when it reached 4 plus (1:32) the intravenous administration of amphotericin B was started. This was given in a dosage of 12 to 15 mg. every twenty-four hours over a period of eighty days for a total dosage of 9.9 gm. Amphotericin B serum levels varied from 1.0 to 6.0 μg./ml. with determinations being made twenty-four hours after administration. The blood urea nitrogen varied from 13.5 mg. per cent to a high of 52 mg. per cent after treatment. At the close of treatment the complement fixation was reduced slightly to 3 plus (1:32), with clearing of the pneumonitis and decrease of the lung root adenopathy. (Fig. 4B.) Three months after therapy the patient remains well, is physically active, and complement fixation has fallen to 3 plus (1:16).

Comments: The severity of the illness in this case, accompanied by a rising complement fixation titer to 4 plus (1:32), provided indication for prompt use of intravenously administered amphotericin B in full dosage to prevent possible dissemination. Three months after completion of therapy the patient remains well. There has been clearing of the lungs and stabilization of the complement fixation at 3 plus (1:16), (February 10).

Along with antibiotic therapy, administered either intravenously or intrathecally, we have applied the principles of surgical drainage, excision, or elimination of peripheral foci, as seemed indicated. In coccidioidal meningitis this implies frequent lumbar taps, both for drainage of cerebrospinal fluid and control of pressures, as well as the administration of amphotericin B. The reports of six cases of coccidioidal meningitis treated with amphotericin B, five of which received both intravenous and intrathecal administration of the antibiotic now follow (Cases 10 to 15 inclusive):

CASE 10. C. K., a fifty-five year old white male farmer, was admitted with a draining scrotal abscess of two weeks' duration. Examination revealed bilateral epididymal swellings. A chest roentgenogram disclosed only a discrete nodular density in the left lung. The patient also had diabetes mellitus. A coccidioidin skin test was 1 plus (1:100) and the complement fixation 2 plus (1:256). A two months' course of intravenously administered aminostilbamidine (250 mg. per administration) followed, but the complement fixation titer rose to 1 plus (1:512). Two months after admission a bilateral epididymectomy was performed, cultures of the drainage having been positive for C. immitis. Six weeks later the scrotal drainage reappeared, and was associated with bilateral inguinal adenopathy. Two weeks later a right orchiectomy was performed, and at this time the patient was started on amphotericin B administered intravenously. A dosage of 40 to 80 mg. was

given every forty-eight hours for a period of 127 days for a total dosage of 4.66 gm. Four weeks following this operation, meningeal symptoms developed, and examination of the spinal fluid revealed a complement fixation of 4 plus (1:2). The cytology was 1,188/cu. mm., quantitative protein 185 mg. per cent. A single intraspinal injection of 1 mg. of amphotericin B was then given but resulted in severe pain and was not repeated. The amphotericin B blood serum level varied from 1.0 to 5.5 μg./ml., based on determinations forty-eight hours after administration of amphotericin B. The blood urea nitrogen varied from 35 to 62 mg. per cent, falling to 25 mg. per cent after treatment. The complement fixation dropped to 4 plus (1:64) after therapy, where it remained stabilized. The spinal fluid complement fixation became negative fourteen weeks after the start of treatment. Clinical improvement continued, and the patient remains well and active nineteen months after therapy, and the spinal fluid findings are negative.

Comments: This is a case of disseminating coccidioidomycosis with genitourinary involvement, and eventual extension to the meninges following surgical manipulation. Intravenous aminostilbamidine therapy was ineffective. The failure of intravenous amphotericin B therapy is also demonstrated, started only one day previous to right orchiectomy to provide effective "coverage," as indicated by the clinical appearance of coccidioidal meningitis twenty-eight days postoperatively. Sufficient suppressive effect resulted, however, from intensive and long continued intravenous administration of amphotericin B. Final recovery appears established and the patient remains well and at home nineteen months after termination of treatment. This case emphasizes the need for effective coverage during any surgical approach to coccidioidal infection, which apparently requires a one to two month period of administration prior to the surgical procedure.

Case 11. M. C., a five year old white girl, was admitted with a history of respiratory infection two months previously, followed by three weeks of persistent headache, lethargy and temperature of 102°F. There was early bilateral papilledema. A coccidioidin skin test was positive 3 plus (1:100), and a P.P.D. (intermediate) intracutaneous test was negative. A blood serum complement fixation was 2 plus (1:4) with precipitins 4 plus (undiluted). A lumbar puncture revealed slightly cloudy cerebral spinal fluid with an initial pressure of 420 mm. The cells varied from 109 to 201/cu. mm., and the glucose fell to 26 mg. per cent nine days later. The spinal fluid complement fixation was negative. A diagnosis of coccidioidal meningitis was made and the patient was started on amphotericin B, administered intravenously which was given in an average dose of 20 mg. every forty-eight hours, continued for a period of sixty-nine days for a total dosage of 0.75 gm. The serum level varied from 1.0 to 3.0 μg./ml. as determined forty-eight hours after administration. The blood urea nitrogen rose from 9 to 42 mg. per cent and then returned to 10 mg. per cent after treatment. The blood serum complement fixation fell to 1 plus (1:8) three months after completion of therapy. All spinal fluid abnormalities improved under the therapy except the pressures, which remained elevated. The patient was permitted to return home under a regimen of repeated lumbar taps to control the intraspinal pressures. A local physician, instead, inserted a polyethylene catheter into the lower spinal canal, which resulted in a complicating secondary Staphylococcus aureus meningitis. The patient was readmitted in an extremely ill condition. Recovery followed intravenous administration of a series of antibiotics given over the next three weeks, selected according to sensitivity studies of the staphylococcus organism. One month later intrathecal administration of amphotericin B was started, the drug being given every forty-eight hours in a dosage not exceeding 0.4 mg., over an 80 day period, for a total dosage of 11.83 mg. The spinal fluid slowly returned to normal, and the patient was discharged home four months after the second admission. Eleven months after treatment she continued well and repeat spinal fluid studies are essentially negative. The final blood serum complement fixation is 2 plus (1:4).

Comments: In this instance nine weeks of intravenous amphotericin B therapy resulted in partial clinical recovery, but the cerebrospinal fluid pressures remained elevated and some cells persisted. The subsequent occurrence of Staphylococcus aureus meningitis had no adverse effect on the underlying coccidioidal disease. Following recovery from this intercurrent infection a course of intrathecally administered amphotericin B was started, resulting in gradual reversal of the abnormal changes in spinal fluid. The patient became fully ambulatory and remains well and able to continue her school work eleven months after completion of therapy.

Case 12. P. T., an eleven year old school girl, was admitted acutely ill with a history of persistent fever and headache of four to five months' duration. Pulmonary disease was demonstrated by roentgenograms taken three months previously, and an x-ray film taken on admission revealed residual pneumonitis in the upper lobe of the left lung. Following admission hyperactive deep reflexes appeared, and on the third

day the patient had a convulsive seizure with marked rigidity of the neck, followed by the development of opisthotonos. A lumbar tap revealed slightly turbid spinal fluid under 240 mm. of pressure. There were 866 cells/cu. mm. (32 per cent polymorphonuclears), with a protein of 350 mg. per cent, glucose 18 mg. per cent. The spinal fluid complement fixation was 2 plus (1:32), the serum complement fixation was 3 plus (1:16). A coccidioidin skin test was positive. The intravenous administration of amphotericin B was started shortly after admission, and was given every twenty-four or forty-eight hours with a dosage of 40 to 45 mg. for a total of fifty-one days; the total dosage given was 1.69 gm. This was followed by serum levels of 0.3 to 1.0 μg./ml. (determinations made twenty-four to forty-eight hours after administration). The blood urea nitrogen varied from 13.5 to 25.5 mg. per cent, returning to a final level of 14.5 mg. per cent. The serum complement fixation fell to 2 plus (1:16) after therapy. Intrathecal administration of amphotericin B was started five weeks after admission, in dosages up to 0.5 mg. every forty-eight hours, for a period of seventy days and a total dosage of 18.71 mg. This was followed by a reduction in the titer of the spinal fluid complement fixation to 4 plus (1:2). There was continued slow improvement in the other spinal fluid findings and the complement fixation became negative seven months after beginning intrathecal treatment. The patient remains well one year after treatment with no residual changes in the lungs or central nervous system, and the serum complement fixation remains at 4 plus (1:8).

Comments: Severe coccidioidal meningitis in this instance responded completely to the intravenous and intrathecal administration of amphotericin B. The child is well one year after completion of treatment, with no residual changes in the central nervous system. The cerebrospinal fluid cytology, glucose, protein values and manometric pressure readings are normal.

CASE 13. J. W., a thirty-three year old white man, was admitted acutely ill with a history of upper respiratory infection occurring eight weeks' previously, followed by severe persistent headache of one week's duration, stiffness of the neck, and vomiting. The temperature was 100.4°F. Chest roentgenograms revealed a clearing pneumonitis in the lower lobe of the left lung and residual adenopathy in the left hilum. A coccidioidin skin test was positive in 1:100 dilution, the serum complement fixation was 2 plus (1:16). A lumbar puncture yielded slightly turbid fluid under 460 mm. pressure, which contained 674 cells/cu. mm. (30 per cent polymorphonuclears), protein 154 mg. per cent, glucose 38 mg. per cent. The spinal fluid complement fixation was 4 plus (1:2). A culture of the spinal fluid was positive for C. immitis. Amphotericin B was given intravenously for seventy days at forty-eight hour intervals in a dosage of 75 to 80 mg. for a total dosage of 2.1 gm. The blood serum level varied from 0.6 to 4.0 μg./ml., thirty-six to forty-eight hours after administration. The blood urea nitrogen level varied from 14 mg. per cent to a high of 84 mg. per cent, falling to 14 mg. per cent after treatment. The serum complement fixation fell to 4 plus (1:8), the spinal fluid complement fixation remained at 4 plus (1:4).

One month after discharge from the hospital meningeal symptoms recurred. Following readmission there was an upward rise of the serum complement fixation to 1 plus (1:16). Intravenous and intrathecal amphotericin B therapy was given concomitantly, the former in a dosage of 40 to 50 mg. every forty-eight hours for the next thirty-three days for a total dosage of 0.57 gm. No demonstrable serum drug levels were obtained. The blood urea nitrogen levels varied from 14 to 26 mg. per cent. After treatment the serum complement fixation remained at 4 plus (1:16). Intrathecal therapy, given at the same time, consisted of a usual dosage of 0.5 mg. approximately every forty-eight hours, for 170 days, for a total dosage of 31.1 mg. On one occasion a spinal fluid level of 0.6 μg./ml. was obtained forty-eight hours after administration. At the close of this combined therapy the complement fixation was reduced from 4 plus to 1 plus (1:4). The spinal fluid pressures remained elevated and the number of cells persisted at 318/cu. mm., although protein fell to 97 mg. per cent and the glucose rose to 53 mg. per cent. There was sufficient clinical improvement to warrant discharge home. However, recurrence of vomiting and headache one month later returned the patient to the hospital, and repeated spinal studies revealed reactivation of the coccidioidal meningitis manifested by increased pressures of 420 mm., 550 cells/cu. mm., protein 158 mg. per cent, glucose 40 mg. per cent. A culture was positive for C. immitis. The spinal fluid complement fixation was 4 plus (1:4). Intrathecal administration of amphotericin B was again started, concomitantly with intravenous administration, in a dosage of 0.5 mg. injected intraspinally every forty-eight to seventy-two hours for the next eighty-four days for a total dosage of 13.32 mg. Intravenous administration consisted of 70 to 75 mg. given approximately every twenty-four hours for the next 118 days for a total dosage of 7.7 gm. Blood serum levels varied from 1.5 to 12 μg./ml., twenty-four hours after intravenous administration. The blood urea nitrogen rose from 13.5 to 101 mg. per cent, later receding to 29 mg. per cent. The blood serum complement fixation remained stabilized at 3 plus (1:16), and the spinal fluid complement fixation remained at 4 plus (1:4). Toward the termination of the intrathecal therapy, a complicating arachnoiditis prevented regular administration of amphotericin B.

Comments: In this instance of severe coccidioidal meningitis following primary pneumonitis, 10.37 gm. of amphotericin B administered intravenously and 44.42 mg. administered intrathecally resulted in clinical improvement. Development of a complicating arachnoiditis precluded further intrathecal therapy. It is presumed that the cerebrospinal fluid findings are now in part due to the residual arachnoiditis, although this had cleared symptomatically. The patient remains well two months after discharge and is physically active, but a longer follow-up will be necessary to judge the outcome.

CASE 14. S. C., a forty-nine year old white man, was admitted chronically ill, complaining of headache, neckache and vertigo of approximately two and a half years' duration. Coccidioidal meningitis had been diagnosed at another clinic and he had received intermittent intravenous amphotericin B therapy for ten weeks without improvement. There was a weight loss of 35 pounds. Chest roentgenograms revealed no active pulmonary disease. A lumbar puncture disclosed slightly turbid spinal fluid under pressure of 160 mm., with 735 cells/cu. mm., protein 480 mg. per cent and glucose 28 mg. per cent. The spinal fluid complement fixation was 4 plus (1:2). Concomitant intravenous and intrathecal amphotericin B therapy was instituted, the former being given in an average dose of 1 mg./kg. every twenty-four hours for a period of forty-four days for a total dosage of 2.2 gm.; the latter consisted of intraspinal administration of 0.5 to 0.6 mg. every forty-eight hours for forty-two days for a total dosage of 14.2 mg. Amphotericin B levels in the blood serum varied from 1.5 to 3.0 μg./ml., determinations being made twenty-four hours after administration. The blood urea nitrogen varied from 10 to 40 mg. per cent, returning to normal after treatment. Spinal fluid amphotericin B levels were demonstrated on several occasions, varying from 1.0 to 1.5 μg./ml. as determined twenty-four hours after administration. The spinal fluid complement fixation became negative five weeks after the start of therapy, as did the blood serum complement fixation. The patient showed marked clinical improvement and was discharged home, free of headache, neckache and vertigo, and fully ambulatory. He has remained well and asymptomatic for one month following discharge and spinal fluid and blood serum complement fixation remains negative (July 29, 1959).

Comments: In this case chronic coccidioidal meningitis responded strikingly to combined intravenous and intrathecal amphotericin B therapy, the complement fixation becoming entirely negative in both serum and cerebrospinal fluid.

CASE 15. F. C., a nineteen year old male Mexican, was admitted acutely ill with a temperature of 102.6°F., and a history of six weeks' fever, night sweats and chest pain. Chest roentgenograms disclosed pneumonitis in the lower lobe of the left lung with secondary hilar adenopathy. A coccidioidin skin test was negative (1:100). The serum complement fixation was 4 plus (1:32), rising to 3 plus (1:128) in the next three weeks. Amphotericin B was given intravenously every twenty-four or forty-eight hours, the patient receiving 1 mg./kg. for sixty-two days for a total dosage of 2.5 gm. On one occasion a serum level of 0.3 μg./ml. was obtained twenty-four hours after administration. The blood urea nitrogen reached a high of 28 mg. per cent, receding after treatment. There was some clinical improvement and the complement fixation fell to 1 plus (1:64). The patient was discharged home, but eight weeks later fever and headache developed and he was readmitted to the hospital. The chest roentgenogram revealed clearing of the pneumonitis in the lower lobe of the left lung and no residual lung root adenopathy. A repeat coccidioidin skin test was 2 plus (1:10), the blood serum complement fixation had risen to 2 plus (1:128). A second course of amphotericin B therapy was started in a dosage of at least 1 mg./kg. given every twenty-four hours for a total dosage of 5.94 gm. to date. Serum levels have varied from 1.5 to 6.0 μg./ml., determined twenty-four hours after administration. A lumbar puncture on admission revealed turbid spinal fluid under a pressure of 600 mm., 2,370 cells/cu. mm., protein 370 mg. per cent, glucose 30 mg. per cent. Cultures of the spinal fluid were positive for C. immitis. The intrathecal administration of amphotericin B was started on the day following readmission and was given every forty-eight hours at first, just prior to concomitant intravenous therapy. A minimal dose of 0.5 mg. has been given each time, although the frequency has been decreased recently to every seventy-two hours. A total dosage of 2,800 mg. has been given to date. Three and a half months after therapy the skin sensitivity to coccidioidin increased to 1 plus (1:100). Examination of the spinal fluid, four months after beginning therapy, disclosed 81 cells/cu. mm. (52 per cent lymphocytes), protein 110 mg. per cent and glucose 47 mg. per cent. Cultures of the spinal fluid have remained negative for C. immitis since the fourth day of intrathecal therapy. The blood serum complement fixation has fallen to 2 plus (1:64) and the complement fixation in spinal fluid has been reduced to 3 plus (1:8) after reaching a high of 1 plus (1:64) (six weeks after beginning intrathecal therapy). Clinically, the patient continues to improve but still receives both intravenous and intrathecal amphotericin B therapy.

Comments: Severe primary coccidioidomycosis and pulmonary involvement in this case, accompanied by anergy to coccidioidin and a high

TABLE V

RESULTS OF AMPHOTERICIN B THERAPY IN COCCIDIOIDAL MENINGITIS (SIX CASES)

Case	Age (yr.)	Condition	Time Since Therapy (mo.)	Residual Changes	Results
C. K.	55	Well, working	18	Spinal fluid negative, no defects in central nervous system	Excellent
P. T.	11	Well, attending school	11	Spinal fluid negative, no defects in central nervous system	Excellent
M. C.	5	Well, attending school	10	Spinal fluid negative, no defects in central nervous system	Excellent
J. W.	33	Improved, at home	3	Spinal fluid still abnormal, no symptoms of central nervous system defects; on 5/12/59 complement fixation: Serological titer 2+, 1:32; cerebral spinal fluid titer, 4+, 1:4	Inconclusive
F. C.	19	Improved, in hospital	Under intravenous and intrathecal therapy eleven weeks (started on 3/10/59)	No symptoms of central nervous system defects; cultures of cerebral spinal fluid became negative for C. immitis 3/20/59	Improved
S. C.	49	Marked improvement, discharged 6/30/59	Under intravenous and intrathecal therapy from 4/30/59 to 6/13/59	Marked relief of symptoms of central nervous system: headache, neckache, vertigo	Complete reversion of complement fixation titer: Serological titer; 4+, 1:2 to negative; cerebral spinal fluid titer, 4+, 1:2 to negative; normal cerebral spinal fluid

titer of complement fixation, responded to the first course of intravenous amphotericin B therapy, and the complement fixation decreased to 1 plus (1:64). However, two and a half months later coccidioidal meningitis developed. This case also illustrates how well the intravenous and intrathecal administration of amphotericin B is tolerated, under maximum dosage, and the intensity of treatment required for severe coccidioidal meningitis. A return of skin sensitivity to coccidioidin is favorable. Continuation of treatment (both intravenous and intrathecal) is indicated for an indefinite period.

As indicated in Table v, three of these patients can be considered to have had sufficient follow-up to demonstrate definite recovery. The remaining three will require further follow-up and observation, although there has been marked symptomatic improvement following amphotericin B treatment.

The seven cases comprising the next group illustrate the response of a variety of coccidioidal infections to amphotericin B therapy (Cases 16 to 22 inclusive).

CASE 16. L. F. C., a seventy-five year old white man, was admitted with a six month history of superficial granulomatous abscesses over the sternum, chest wall and lower extremities. (Fig. 5A.) Cultures from these areas were positive for C. immitis. A chest roentgenogram revealed infiltration in the right apex (with sputum positive for tubercle bacilli). A coccidioidin skin test was negative (1:10), blood serum complement fixation 2 plus (1:64). In addition to antimicrobial therapy for pulmonary tuberculosis, the patient was given amphotericin B intravenously, every forty-eight hours in a minimum dosage of 1 mg./kg. for ninety-one days for a total dosage of 3.1 gm. Blood serum levels of 1.0 to 3.0 μg./ml. were demonstrated forty-eight hours after intravenous administration. The blood urea nitrogen reached a high of 25 mg. per cent. By the sixth week after initiation of

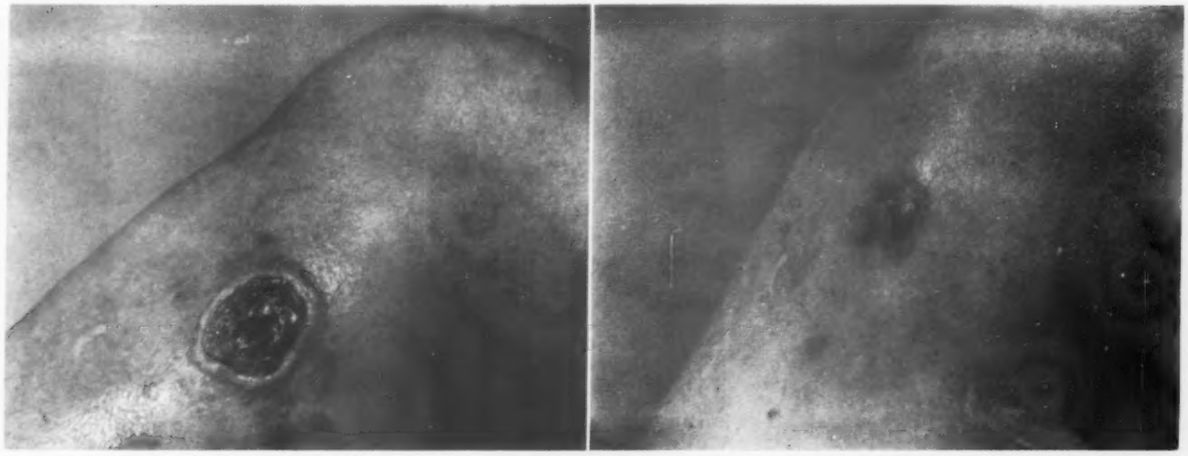


FIG. 5. Case 16. Superficial coccidioidal ulcer with granulomatous center and indurated edges. Lateral surface, left leg. Cultures from exudate positive for C. immitis. *Left*, before treatment. *Right*, after twenty-four days of intravenous amphotericin B therapy.

treatment there was good healing of all peripheral abscesses and no further drainage was evident. The patient became skin sensitive to coccidioidin at the end of the third week, 2 plus (1:10). Following therapy the complement fixation fell to 3 plus (1:32). One year after admission the patient was discharged home with inactive tuberculosis and maintained healing of the superficial coccidioidal abscesses. Thirteen months after completion of therapy the complement fixation had decreased to 2 plus (1:2), and the patient remained normally active at home.

Comments: In this case there was rapid healing of coccidioidal abscesses, sinuses and ulcerations, within a month after institution of intravenous amphotericin B therapy. The favorable serologic changes and return of skin sensitivity to coccidioidin also indicated the effectiveness of treatment in this patient.

CASE 17. R. O., a fifty-two year old white housewife, was admitted acutely ill, with a temperature of 101.2°F. A respiratory infection occurring seven months previously was followed by the development of multiple peripheral abscesses (the actual count was 68 open shallow lesions, widely distributed over the entire body). Biopsy specimen and cultures were positive for C. immitis. A coccidioidin skin test was negative (1:10), the blood serum gave an incomplete complement fixation 2 plus (1:128). Long courses of hydroxystilbamidine and aminostilbamidine administered intravenously were ineffective and the patient's body weight decreased from 110 to 75 pounds. Repeated cauterization of the multiple abscesses, supplemented by surgical drainage, resulted in clinical improvement and was followed by a return of skin sensitivity to coccidioidin (1:10), five months after admission. After discharge and being at home for four and a half months she was readmitted with complaints of tachycardia, low grade fever (99.4°F.) and cardiac pain. A chest roentgenogram disclosed generalized cardiac enlargement, and electrocardiograms revealed abnormal changes in the T wave. Complement fixation had increased from 2 plus (1:32) to 4 plus (1:64). A diagnosis of coccidioidal myocarditis was made and amphotericin B was given intravenously, but only for a short time due to the considerable venous thrombosis resulting from the previous stilbamidine therapy. A total of 0.79 gm. of amphotericin B was injected, in small doses every forty-eight hours over a period of thirty days; this was supplemented with the oral administration of amphotericin B, 3 gm. daily, for seventeen days. Bed rest and oxygen therapy were included. Clinical improvement occurred and she was discharged three and a half months after admission. Twenty-one months after therapy she remained well and active at home. Recently, a recurrent granulomatous abscess appeared on the lower right leg. This is responding to local treatment, including surgical drainage and cauterization, together with the intravenous administration of amphotericin B. The last complement fixation remained at 2 plus (1:32).

Comments: Extensive skin granulomas and peripheral abscesses showed little response to stilbamidine derivatives, although repeated cauterization of these lesions with the high frequency current appeared beneficial. An ensuing coccidioidal myocarditis was controlled by short term intravenous amphotericin B therapy and this was followed by stabilization and lowering of the titer of complement fixation. The patient remained well and active twenty-one months after therapy. A recurrent coccidioidal abscess on the lower right leg is responding to treatment.

CASE 18. E. M., a twenty-one year old Mexican woman, was admitted only moderately ill but with an ulcerated lesion of the left thigh of five months' duration. Secondary inguinal adenopathy was noted on the left side. Biopsy established the presence of coccidioidal infection. Although a respiratory illness had been present one month before the appearance of the granulomatous ulcer, a chest roentgenogam taken at the time of admission was negative. The coccidioidin skin test was positive, the blood serum complement fixation was 3 plus (1:16). Amphotericin B, administered intravenously, was started with a dosage of 1 mg./kg., and continued every twenty-four hours for thirty days for a total dosage of 1.22 gm. The blood serum level varied from 3.0 to 6.0 μg./ml. taken twenty-four hours after administration. The blood urea nitrogen reached a high of 33.5 mg. per cent. The area of ulceration was cauterized on one occasion with the high frequency electrical current; this was done before the institution of amphotericin B therapy, and produced no visible healing. Three weeks after initiation of amphotericin B therapy healing became apparent. The complement fixation decreased to 2 plus (1:4) following this therapy, and three months later the patient remains well at home. Complete healing of the ulcerated skin area has been maintained.

Comments: High frequency electrical cauterization alone was not sufficient to effect healing of chronic ulcerative skin granulomas of the coccidioidal type. A combination of amphotericin B and cauterization was much more effective. Complete healing has occurred and this patient remains well three months after therapy.

CASE 19. R. McM., a fifty-four year old white man, was admitted moderately ill. Seven months previously he had had fever, malaise, and the formation of four deep abscesses which appeared and drained in the right lumbar, inguinal and suprapubic areas. Surgical incision of these abscesses by his private physician resulted in chronic sinuses and persistent purulent drainage which remained positive by culture for C. immitis. A coccidioidin skin test was negative (1:100), the complement fixation was 4 plus (1:128). Amphotericin B was given intravenously every twenty-four or forty-eight hours in a dosage of 1 mg./kg. for seventy days for a total dosage of 2.79 gm. The serum drug levels varied from 1.0 to 1.5 μg./ml. in determinations made forty-eight hours after administration of amphotericin B. The blood urea nitrogen reached a high of 37 mg. per cent, but returned to a normal of 13 mg. per cent after treatment. Two weeks after institution of therapy there was beginning closure of the sinuses and toward the end of the second month of therapy fairly complete healing became evident. The serum complement fixation fell to 1 plus (1:128). Six months after completing treatment the patient remains well at home and there has been no evidence of recurrence of the abscesses or sinuses. The complement fixation has continued to decrease to 4 plus (1:64). He is now skin sensitive to coccidioidin 1 plus (1:100).

Comments: Complete healing of deep sinuses and underlying abscesses did not occur until amphotericin B was administered intravenously, surgical drainage alone having been insufficient for control of the deep abscesses. Healing of the abscesses was also followed by a favorable serologic change. The patient remains completely well six months after completion of therapy and has returned to active work. Previous skin anergy to coccidioidin has been reversed, and complement fixation has decreased to 4 plus (1:64).

CASE 20. G. B., a forty-four year old white woman, was admitted with known coccidioidal disease of several years' duration, accompanied by chronic cough, dyspnea and weakness. A chest roentgenogram revealed destruction of the entire left lung, a large cavity replacing the upper lobe. (Fig. 6A.) The sputum was positive for C. immitis. A coccidioidin skin test was positive, the serum complement fixation was 2 plus (1:128). Preoperatively, amphotericin B was administered intravenously, twenty-eight doses in a period of sixty-four days for a total dosage of 0.77 gm. A left extrapleural thoracoplasty was then performed preliminary to left pneumonectomy; the latter procedure was carried out three months after the primary thoracoplasty. During pneumonectomy, the large cavity was inadvertently torn and the chest space subjected to contamination by cavity content. Despite this, uneventful postoperative healing occurred (Fig. 6B), coincident with a short term postoperative course of amphotericin B given intravenously over a period of fourteen days, in a dosage of 60 mg. every twenty-four hours for a total dosage of 0.68 gm. Following this, the complement fixation decreased to 2 plus (1:64). Eight months after completion of therapy the patient remains well and asymptomatic at home, engaged in household duties, and the complement fixation has decreased to 3 plus (1:32).

Comments: In this case there was extensive pulmonary coccidioidal disease, resulting in total destruction of the left lung. Anticipating the necessity of surgical removal of this lung, the preoperative preparation included a two month course of intravenous amphotericin B therapy. This was followed by definite clinical improvement and reduction of cough and sputum, the latter having been positive for C. immitis. Coverage was also provided postoperatively. Despite contamination of the pleural

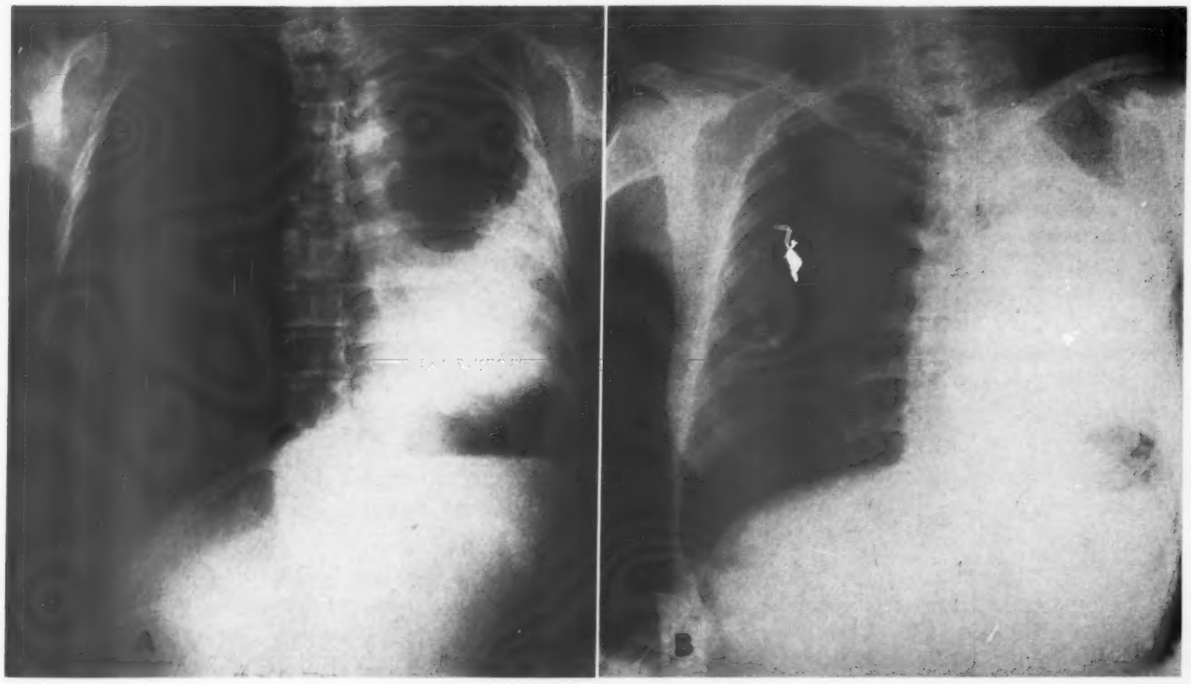


FIG. 6. Case 20. A, before treatment. B, three and a half months postoperatively.

space during surgery by cavity content, no postoperative complications occurred. The papatient is well and active one year following surgery. The effectiveness of amphotericin B as a covering agent for pulmonary resection is thus demonstrated.

CASE 21. V. E., a fifty-seven year old Filipino man, was admitted for treatment of pulmonary cavitation of the residual coccidioidal type. He complained of cough and small repeated hemoptyses of three weeks' duration. Chest roentgenograms revealed a 2.5 cm. thin-walled cavity in the upper lobe of the right lung. A coccidioidin skin test was 1 plus (1:100), the serum complement fixation was 4 plus (1:16). Artificial pneumothorax was instituted to close the cavity but complete collapse of the upper lobe could not be obtained due to intrapleural adhesions. A closed intrapleural pneumolysis was considered feasible but it was considered advisable to precede this by amphotericin B coverage. This was given in a dosage of 1 mg./kg., every forty-eight hours for twenty-four days, requiring eleven administrations for a total dosage of 0.71 gm. There was only a moderate elevation of the blood urea nitrogen. Two and a half weeks after initiation of this therapy a successful pneumolysis was performed. This was followed by closure of the cavity. Following a right phrenic nerve crush and temporary paralysis of the right hemidiaphragm, the pneumothorax was abandoned. Following re-expansion of the collapsed lung, the cavity has remained closed and the patient is well and working twenty months later. The serum complement fixation remains stabilized at 2 plus (1:16).

Comments: Amphotericin B is again shown to provide effective coverage for a limited surgical procedure (closed intrapleural pneumolysis) which, when combined with artificial pneumothorax, resulted in complete closure of a residual pulmonary cavity of the coccidioidal type. The patient remains well and the cavity closed twenty months after completion of this type of collapse therapy under amphotericin B coverage.

CASE 22. L. A. H., a thirty year old white woman, was admitted acutely ill with a temperature of 102°F., associated with cough and pain in the right side of the chest of two weeks' duration. Erythema nodosum had appeared ten days previously. The patient was in the fifth month of pregnancy. A chest roentgenogram revealed pneumonitis involving the lower lobe of the right lung, with secondary hilar adenopathy. A coccidioidin skin test was 4 plus (1:100). A complement fixation of 2 plus (1:8) rose to 3 plus (1:32) and precipitins persisted at 4 plus (1:10). The severity of her primary coccidioidomycosis, complicated by pregnancy and a rising titer of complement fixation, suggested the intravenous administration of amphotericin B. A minimum dosage of 1 mg./kg. was given on a forty-eight hour basis, over a period of sixty-nine days for a total dosage of 1.90 gm. The serum level varied from 0.6 to 6.0 μg./ml. as determined

forty-eight hours after administration. The blood urea nitrogen rose to a high of 47 mg. per cent. Therapy was followed by a decrease in the serum complement fixation to 2 plus (1:8) and the disappearance of precipitins. The patient was discharged home and was delivered of a normal baby nine weeks following completion of amphotericin B coverage. Two years following therapy the patient and baby remain in good health.

Comments: The tendency for primary coccidioidal disease to disseminate during pregnancy has been reported in the literature [*29,30*]. The use of amphotericin B intravenously, as illustrated in this patient, is a safe procedure during pregnancy, and will protect the patient from the dangers of dissemination.

CONCLUSIONS

As a result of these preliminary observations amphotericin B would appear to be the first truly effective agent against coccidioidal disease that has become available. Its use, however, is not simple, and requires perseverance and patient cooperation in order to deliver sufficient dosage to maintain effective serum levels for a period of two to three months, or even longer in severe infections. The mild toxic effects, which appear in most patients, can be minimized by simple control measures. Unless this antibiotic is used aggressively and with determination, serious forms of coccidioidomycosis will continue to result in a high mortality, which should no longer be acceptable.

It may not always be feasible to continue intravenous amphotericin B therapy until definite regression of the titer of complement fixation occurs. Observation of a few of our patients over a period of years has shown that a high and stabilized titer of complement fixation is compatible with permanent recovery and health. However, it will be both reassuring and encouraging to the therapist to obtain regression of an elevated titer of complement fixation as a measure of the effectiveness of amphotericin B therapy. That this may be a slow process, responding only several weeks after manifest clinical improvement and clearing of pulmonary disease, is to be accepted. Following the surgical removal of large segments of pulmonary tissue infected by C. immitis, such as pulmonary cavities, we have seen almost immediate lowering of the complement fixation titer. But this is not always so, and experience has shown that surgical eradication of an entire coccidioidal lesion, as in lobectomy, may not be immediately reflected in reduction of the complement fixation titer.

As in tuberculous disease, every endeavor should be made to discover coccidioidal meningitis as early in its course as possible; this may require lumbar puncture and examination of cerebrospinal fluid during any severe coccidioidal illness. If meningeal involvement occurs, combined and intensive intravenous and intrathecal amphotericin B therapy becomes essential.

SUMMARY

Observations and conclusions based on the use of amphotericin B in nine cases of severe coccidioidal disease with impending or actual dissemination, and six cases of coccidioidal meningitis are recorded, also a study of the effectiveness of this antibiotic in seven patients presenting miscellaneous coccidioidal disease. The latter include peripheral skin granulomas and abscesses, illustrate protective coverage during surgical procedures and, in one instance, prophylactic treatment to prevent possible dissemination of primary coccidioidal infection during pregnancy.

Until a more effective and simpler antibiotic becomes available, amphotericin B provides the therapy of choice against serious forms of coccidioidal disease. With accumulated experience, and over a longer period of observation, will come better evaluation of its use and limitations.

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Littman. To my medical associates and office staff at the Tulare-Kings Counties Hospital, Springville, goes the credit for working up cases and assisting in the long-continued problems of therapy.

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Clinicopathologic Conference

Hemiparesis, Coma and Uremia

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine, and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A THIRTY-SEVEN year old white man (M. W.) entered Barnes Hospital for the first time on August 2, 1958. He died on August 9, 1958.

The patient was comatose when admitted to the Barnes Hospital; his past history was obtained from the referring physician, the patient's wife and father. The patient was believed to have been in good health until one week prior to admission when he was found unconscious after haven fallen out of bed. A right-sided hemiparesis was noted, and the patient was promptly admitted to a local hospital where no evidence of injury to the head was detected. During the following seven days his hospital course was one of progressively deepening coma, with persistence of the right-sided hemiparesis. No lumbar puncture was performed. Because of persistent and deepening coma and the appearance of fever, the patient was transferred to Barnes Hospital for further evaluation.

At twenty-one years of age, the patient was told that he was "hypertensive," but no subsequent follow-up evaluations were made. According to his relatives, the patient never complained of headache, epistaxis, chest pain, or visual difficulties. The patient was known to have been right handed.

One sister had been operated upon at Barnes Hospital in 1945 for a left parieto-occipital subdural hematoma with recovery, except for residual grand mal epilepsy. The patient's mother died of "kidney poisoning." No further details were noted.

On physical examination the temperature was 37.5°C.; respirations, 16 per minute; pulse, 110 per minute and regular; and blood pressure, 150/100 mm. Hg in the right arm, and 155/95 mm. Hg in the left arm with the patient in the supine position. The patient was comatose but there was no evidence of chronic wasting. He responded only to painful stimuli by movement of the left upper and lower extremities. There was no evidence of dehydration. Significant enlargement of the lymph nodes was absent; the back and spine appeared to be normal; and there was no sacral edema. Examination of the extremities revealed no abnormalities. The head was normocephalic without evidence of trauma or postauricular ecchymoses. No cranial murmurs were noted upon auscultation. Examination of the eyes revealed both pupils to be dilated and non-reactive to light. The sclera and conjunctivas were within normal limits. The funduscopic examination revealed fullness of the retinal veins, but no venous pulsations. The retinal vessels were otherwise within normal limits; there were no hemorrhages, exudates or papilledema. Examination of the ear, nose and throat disclosed no abnormalities. There was marked nuchal rigidity. The thorax was symmetrical with bilaterally equal respiratory excursions. On auscultation, there was bilateral scattered rhonchi. The left border of cardiac dullness was at the mid-clavicular line in the fifth intercostal space. The rhythm was regular. The aortic second sound and the pulmonic second sound were of equal intensity. There were no cardiac murmurs. The abdomen was flat. The liver edge was palpated 6 cm. below the right costal margin. There was a large firm, fixed mass which occupied almost the entire upper left quadrant of the abdomen. The mass did not pulsate or move with respiration although assessment was difficult due to the patient's inability to cooperate. Femoral pulses were of good quality and there were no murmurs noted over these vessels. The genitalia and rectal examination were within normal limits. Neurologic examination revealed a comatose male, unresponsive to painful stimuli on the right side, but responsive

TABLE 1
SUMMARY OF LABORATORY DATA

Data	Date					
	8/3	8/4	8/5	8/6	8/7	8/8
Blood:						
Sodium (mEq./L.)	172	....	178	172	165	168
Potassium (mEq./L.)	7.0*	....	4.3	4.5	4.5	4.4
Chloride (mEq./L.)	137	....	137	140	135	.....
CO_2 (mEq./L.)	26.6	....	23.6	26.9	21.5	.....
Non-protein nitrogen (mg. per cent)	102	....	123	111	127	.....
Urine:						
Sodium (mEq./L.)	.....	....	37.0	.....	.....	.....
Potassium (mEq./L.)	.....	....	32.0	.....	.....	.....
Fluid intake (cc./24 hr.):						
Total	1,500	2,500	3,000	2,000	3,000	3,000
Saline	1,000	1,000	.....	.....	.....	.....
Output (cc./24 hr.)	2,200	1,725	1,600	1,475	2,150	2,070

* Blood hemolysed.

to painful stimuli on the left side. There was a right hemiparesis, without evidence of muscle atrophy. The deep tendon reflexes on the right side were less active than those on the left. There were no pathologic toe signs present.

The laboratory data were as follows: Hemoglobin, 16.6 gm. per cent; white blood cells, 12,150 per cu. mm.; differential pattern with band forms, 4 per cent; segmented forms, 84 per cent; lymphocytes, 10 per cent; monocytes, 1 per cent. The platelets appeared adequate. Urinalysis revealed a specific gravity of 1.010, reaction 6.0, with a trace proteinuria, and no reducing substances present. Upon microscopic examination of the urinary sediment, there were many red blood cells and 14 to 16 white blood cells per high power field. Stool guaiac test was negative. The blood non-protein nitrogen was 102 mg. per cent; blood sugar, 104 mg. per cent; sodium, 172 mEq./L.; potassium, 7.0 mEq./L. (hemolyzed blood specimen suspected); chloride, 137 mEq./L.; carbon dioxide combining power, 26.6 mEq./L.; calcium, 10.2 mg. per cent; phosphorus, 4.4 gm. per cent; cholesterol, 205 mg. per cent; total serum protein, 7.2 gm. per cent; with albumin, 4.1 gm. per cent; and globulin, 3.1 gm. per cent. Several blood sugar determinations revealed elevated values, however these samples were taken at times of glucose infusions. Prothrombin time was 70 per cent of normal. Roentgenographic examination of the skull revealed no abnormalities; examination of the abdomen was technically difficult, but a questionable left mid-abdominal mass was noted. The relationship of the abdominal mass and the left kidney could not be satisfactorily evaluated from this examination. An electrocardiogram was interpreted as indicative of left ventricular strain and sinus tachycardia. Lumbar puncture at time of admission revealed an opening pressure of 350 mm. water, and following the removal of 10 ml. of spinal fluid the pressure was 135 mm. water. The fluid was markedly xanthochromic in all three tubes. Cells without acid were 9,792 per cu. mm., 97 per cent of which were crenated; and 18 cells per cu. mm. with acid. Spinal fluid protein was 142 mg. per cent; sugar, 66 mg. per cent; and chloride, 148 mEq./L. Colloidal gold and serologic tests for syphilis were negative. The spinal fluid glutamic oxaloacetic transaminase was 36 units. Additional laboratory data may be noted in Table 1.

A neurosurgical consultant advised against craniotomy since such a procedure had little to offer therapeutically and would only contribute to further deterioration. The patient was maintained on supportive therapy including the administration of parenteral fluids, oxygen, antibiotics, and routine physical measures. Despite these procedures, he remained febrile throughout his hospital course with temperature elevations varying between 38° and 39°c. Intermittent episodes of restlessness appeared during

the first few days of hospitalization but the patient lapsed into a progressively deeper coma. On August 4, 1958 hemoglobin was 17.5 gm. per cent; white blood cells, 14,000 per cu. mm.; differential pattern of eosinophils, 1 per cent; band forms, 6 per cent; segmented forms, 62 per cent; lymphocytes, 25 per cent; monocytes, 7 per cent. During the last day of the patient's life the temperature rose to 40°c., the pulse became intermittently irregular with rates varying between 120 per minute and 54 per minute, and Cheyne-Stokes respirations appeared. Examination at this time revealed diminished breath sounds at the right posterior thorax without rales or dullness upon percussion. Neurologic examination remained unchanged from that noted at the time of admission. Terminally, the patient's blood pressure rose to levels greater than 300/150 mm. Hg, and then fell precipitously to hypotensive levels. The hypotension did not respond to therapy with Vasoxyl,® and the patient died.

CLINICAL DISCUSSION

DR. SOL SHERRY: Our patient was a thirty-seven year old white man who was asymptomatic until two weeks before his death when he had a sudden onset of unconsciousness and right hemiparesis. He remained in coma until his death two weeks later. Two points of special note in his past history were that hypertension was noted at the age of twenty-one and that his mother died of kidney poisoning. After one week of hospitalization elsewhere, he was transferred to Barnes Hospital where, in addition to his comatose state and right hemiparesis, he was noted to have dilated pupils, a stiff neck, sensory loss and diminished reflexes on the right side. A large, firm, fixed mass filled the upper left quadrant of the abdomen and a mass interpreted as liver was felt in the upper right quadrant. Significant laboratory data included a spinal fluid with increased pressure, marked xanthochromia and an increased number of red cells. Other findings included azotemia, hematuria, mild polycythemia, hypernatremia and hyperchloremia. He became progressively more comatose, ran a persistent febrile course and on the last day of his illness the temperature rose to 40°c., the pulse became irregular, the blood pressure first rose to levels greater than 300 and then fell precipitously. The hypotension did not respond to therapy with Vasoxyl. Dr. Hodges, would you discuss the roentgenograms at this time?

DR. FRED HODGES: Roentgenographic examinations of the head and abdomen were difficult because of coma, but fairly satisfactory films of the skull and a single supine anteroposterior view of the abdomen were obtained.

The films of the skull show a faintly calcified pineal gland in the lateral view which was not discernable in the frontal projection. There was no other intracranial calcification. The bony calvarium and the base of the skull were normal as was the sella turcica.

The single film of the abdomen demonstrated usual gas shadows. Neither renal shadow was completely outlined, but the left psoas shadow was normal. There was a suggestion of an increased mass of soft tissues in the upper part of the abdomen but there was nothing to indicate which organs were involved.

In summary, these films failed to demonstrate a definite abnormality although they did suggest a soft tissue enlargement in the upper part of the abdomen. There was no radiographic evidence to suggest intracranial disease.

DR. SHERRY: Let us at this point confine our attention to the nature of the cerebral lesion in this patient. I wonder, Dr. Berg, whether you might begin the discussion by telling us what you consider the differential diagnosis.

DR. LEONARD BERG: The chief neurologic features were sudden coma, a right hemiparesis to hemiplegia, increased pressure, xanthochromia and blood in the spinal fluid. There is scarcely any doubt that the patient had an intracerebral hematoma in the left cerebral hemisphere. The marked hemiplegia and the hemisensory loss, both suggest that the accumulation of blood was within the hemisphere, fairly deep in the hemisphere probably, and not due to accumulation of blood externally as by subdural or epidural hemitoma. I do not believe there was any relation to the injury to the head suffered in the fall. A sudden intracerebral hematoma, nontraumatic, in a thirty-seven year old man with mild hypertension is most likely due to rupture of a berry aneurysm. From the hemiplegia and hemisensory loss one would presume that this aneurysm might be at the bifurcation of the internal carotid or on the proximal portion of the middle cerebral artery with rupture deep into the hemisphere. Rarer causes of intracerebral hematoma in a patient such as this would be (1) a simple hypertensive hemorrhage,

(2) hemorrhage from another type of vascular anomaly, namely, an arteriovenous malformation, (3) hemorrhage into or around a malignant brain tumor either primary or metastatic, (4) hemorrhage from an arteritis, and (5) hemorrhage due to blood dyscrasia. From the neurologic point of view we have no evidence that can help us to distinguish among these, except that statistically a rupture from a berry aneurysm would be most likely.

DR. SHERRY: Dr. Rosenbaum, would you agree with this interpretation?

DR. HERBERT ROSENBAUM: I think that percentagewise, in this age group, a ruptured aneurysm certainly would be most probable. However, it is impossible to exclude the other causes of spontaneous hemorrhage on the basis of the information given. It is noteworthy that certain physical signs often present in hemorrhage from aneurysms, such as hemorrhages into the retina, were absent here. Other findings that were not present that might be very helpful are vascular abnormalities in the retinal vessels. The absence of a bruit is again negative evidence toward the presence of a fistulous malformation, but I see no way in which one can come to a logical conclusion that only a berry aneurysm should be considered to the exclusion of other reasons for hemorrhage.

DR. SHERRY: Apparently then you think the possibility still exists of a primary atherosclerotic lesion which, in association with hypertension, bled.

DR. ROSENBAUM: The finding of normal eye grounds makes it less likely that an advanced atherosclerotic lesion accounts for hemorrhage. I think that we should look elsewhere in the body and also to the family history for some help in arriving at a diagnosis. The mass in the abdomen, of course, cannot be overlooked nor can the familial history of apparent kidney disease. I believe that extracerebral bleeding, if it is of any magnitude, can reproduce this picture in its entirety.

DR. SHERRY: Dr. Berg, do you also consider that this patient had subarachnoid hemorrhage as well as intracerebral hemorrhage?

DR. BERG: The xanthrochromia and the blood in the spinal fluid tell us that there has been some degree of subarachnoid hemorrhage. His immediate deep coma, from which there was no improvement, and the hemiplegia, suggest that the bulk of the bleeding was into the hemisphere.

DR. SHERRY: McDonald and Korb in their article on berry aneurysms* describe the location of 780 odd berry aneurysms. There are several points worthy of comment. First, berry aneurysms occur in the anterior part of the circle of Willis. Second, a common location is at the site of bifurcation, such as the site of bifurcation of the internal carotid, or of the anterior cerebral artery, or off the posterior part of the circle. Third, when these aneurysms rupture, not only may they rupture into the subarachnoid space but they may also rupture into the brain. These aneurysms of the anterior part of the circle of Willis, that is the anterior cerebral arteries and the intercommunicating branches, tend to rupture into the frontal lobe, whereas those of the internal carotid artery or the middle cerebral artery may either rupture into the temporal lobe or actually into the frontal lobes. Thus different neurologic syndromes occur depending upon the location of the ruptured aneurysm. Dr. Berg, if you believe this man most likely had a ruptured berry aneurysm, could you localize the site of hemorrhage a little more closely?

DR. BERG: Well we are limited in the amount of information we can obtain from a comatose patient, but a hemiplegia was described and a hemisensory loss, of such magnitude that he apparently did not feel painful stimuli in the right extremities. If we accept these two points, we must believe that the major projection pathways for both motor power and sensation were involved. This would tend to make us think that the lesion was not in the mid- or forward portion of the frontal lobe but in the posterior frontal lobe or deep involving the internal capsule. It could well be deep temporal or a combination of temporal and posterior frontal lobes. If the patient had been more alert and could have been tested for hemianopsia, this finding would have placed the lesion in the temporal lobe. Presumably, he had no difficulty with his extraocular muscles which would place the lesion in relation to cranial nerves. Based on the bare hemiplegia and hemisensory loss, I would say that the lesion was deep in the midportion of the hemisphere, either temporal, posterior frontal or a combination of the two. Therefore the hemorrhage most likely resulted from an aneurysm at the bifurcation of the internal carotid or in the proximal portion of the middle cerebral artery.

* MCDONALD, C. A. and KORB, M. Intracranial aneurysms. *Arch. Neurol. & Psychiat.*, 42: 298, 1939.

DR. IRWIN LEVY: For the sake of completeness, I think it should be pointed out that aneurysms of the posterior cerebral vessel also rupture into the temporal lobe and can give a picture similar to this.

DR. SHERRY: Dr. Levy, one of the considerations in this case will be whether or not there was an actual hypothalamic lesion which may have been partly responsible for the hypernatremia exhibited by this patient. I wonder whether rupture of any of these vessels, more likely than others, would lead to such a lesion?

DR. LEVY: I do not believe so since all the branches of the circle of Willis send twigs into the hypothalamus, and in any aneurysm, or actually any lesion giving a subarachnoid hemorrhage, one could interfere with blood supply in the hypothalamus. However, it is not essential to have a lesion in the hypothalamus to produce hypernatremia.

DR. SHERRY: Dr. Berg, let me ask one more question about this problem. Some people believe that these aneurysms are more likely to dissect than rupture; others believe that they actually rupture and that massive hemorrhage occurs. Does thrombosis occur in association with or subsequent to the rupture or dissection, and can this account in part for some of the symptoms which this patient presented?

DR. BERG: Yes, disturbance of circulation in the distribution of the parent vessel does account for some clinical manifestations of berry aneurysms. Spasm of the parent vessel and also occlusion have been seen. The profound coma, the completeness of the hemiplegia and hemisensory loss would be more in favor of the concept that it is the hemorrhage producing the symptoms rather than infarction.

DR. SHERRY: Then it would not surprise you to see some thrombosis and infarction as well as hemorrhage?

DR. BERG: They are common accompaniments.

DR. SHERRY: Dr. Bean, do you have any thoughts about the pathogenesis of berry aneurysms, particularly since you are tremendously interested in vascular lesions in general.

DR. WILLIAM BEAN: There have been a great many studies of the problem and there is a fair amount of evidence to suggest the presence of congenital dysplastic anomalies which tend to run in families. They probably represent congenial weak spots frequently at bifurcations of vessels, which clinically do not cause trouble early in life, but only in adult life or after adolescence. They rarely affect people in old age, but then there are plenty of other vascular troubles that do. So beyond saying that there is an inborn weakness of blood vessels I do not believe that there is anything further I can add.

DR. SHERRY: In the studies of sweet pea poisoning, the arterial lesions produced are dissecting aneurysms of the aorta. In addition, to this do lesions similar to berry aneurysms develop in the cerebral vessels of these animals?

DR. BEAN: They have not been studied systematically, but there may be damage to the media of a great many vessels. The lesions may not go on to dissecting aneurysms. I do not believe the brains were examined.

DR. SHERRY: Dr. Goldring, are you willing to accept the diagnosis of a ruptured berry aneurysm in this patient?

DR. SIDNEY GOLDRING: Statistically speaking one would have to say that this man had ruptured a berry aneurysm. The hypertension at age twenty-one, the family history of kidney disease, and the radiologic evidence of a mass in the abdomen, associated with hematuria and elevation of the non-protein nitrogen suggest the presence of complicating congenital kidney disease. I think it is very likely that the incidence of berry aneurysm is higher in such a case than in the uncomplicated case in which we may be dealing with a straightforward cerebral vascular accident and atherosclerotic lesion.

DR. SHERRY: Is the course of this patient entirely compatible with a ruptured berry aneurysm?

DR. GOLDRING: Yes, absolutely.

DR. SHERRY: Would this include the fever and leukocytosis exhibited by this patient?

DR. GOLDRING: Yes, it is true that the patient's temperature was elevated persistently and at high levels throughout the hospital course, but we saw this man, I believe, after the onset of his hemorrhage. He was apparently going downhill and was really in a terminal state. The temperature elevation at this point may be complicated by secondary infection or may even be present on a central basis.

DR. SHERRY: How about the final events when this patient was observed to have a sudden rise in blood pressure, a slow and irregular pulse, and Cheyne-Stokes respirations? Can we relate this to his cerebral lesion?

DR. GOLDRING: Certainly this is the way a patient who decompensates from increased

intracranial pressure dies. First of all, we believe, because of stimulation of the cerebral or the cardiovascular centers in the mid-brain and medulla, that the blood pressure responds by becoming elevated and the pulse responds by becoming slowed. Then, as the intracranial pressure continues to rise, you pass from a stage of irritation or stimulation to a point where the cardiovascular centers decompensate and the patient shows peripheral vascular collapse. The blood pressure drops, the pulse rises, and the patient stops breathing before the heart stops. The heart may continue to beat for anywhere from a few minutes to as long as fifteen minutes and then the patient dies.

DR. SHERRY: Then you believe this was a cerebral death and that it could be attributed to fresh bleeding, or new damage to the brain in association with the underlying vascular lesion.

DR. GOLDRING: I think it is compatible with death due to increased intracranial pressure, most likely in this case due either to continued accumulation of blood and expanding clot or medullary infarction.

DR. SHERRY: It is apparent then that most of the neurologists consider a ruptured berry aneurysm as the most likely diagnosis, but we cannot exclude the possibility of another type of vascular lesion with bleeding from that. Let us then turn to another phase of this problem, that is the rather interesting hypernatremia and hyperchloremia which this patient demonstrated. We are all aware that this is occasionally seen in patients with cerebral disease. I wonder, Dr. Reichlin, if you could comment on this aspect of the case?

DR. SEYMOUR REICHLIN: Although there are a number of physiologic mechanisms by which the nervous system may influence electrolyte metabolism, the best explanation for the abnormalities in this particular case is inadequately treated water deficit in a patient who is unable to perceive or respond to the sensation of thirst because of coma. The increase in plasma sodium chloride and hemoglobin may be taken as an indication of water deficit; uremia may also have been in part due to dehydration of a patient with limited urine concentrating capacity. The combination of neurologic disease and hypernatremia has been frequently described, most often with lesions of the frontal lobe. The brain localization is not specific, however, but common to all cases is a disturbed state of consciousness. This syndrome may occasionally arise as a primary consequence of injury to the brain with diabetes insipidus, but even then coma is a necessary concomitant.

Although water loss is the most likely pathogenic factor in this patient, there has been much speculation about the possibility that in this syndrome areas of the brain affecting urinary electrolyte excretion might be involved. In addition to diencephalic control of the antidiuretic hormone, recent work of Farrell suggests that the diencephalon, particularly the posterior region and the pineal gland, have potent effects on aldosterone output of the adrenal gland in dogs. Further evidence of neurogenic control of aldosterone comes from the finding that emotional stress in man causes an increase in aldosterone secretion. There is also the possibility that the central nervous system contains the volume receptor controlling the extracellular-fluid-volume (ECF) although most workers now believe that the receptor lies within the thoracic cavity.

DR. SHERRY: I agree that this is the usual mechanism in most of the cases of cerebral hypernatremia. Dr. Daughaday, what disturbs me about this particular patient is that he was not described as being dehydrated in spite of the profound hypernatremia, and he persisted in having a good urine output. Now it seems to me that we must invoke other factors than just a derangement in thirst mechanisms. Do you agree?

DR. WILLIAM DAUGHADAY: On occasions we have seen striking exceptions to the usual rule that patients with disease of the central nervous system and electrolyte disorders present primarily with overwhelming lesions. One ambulatory patient, following operation for a craniopharyngioma, apparently was in normal hydration clinically but his serum sodium concentration was in the 170 to 180 mEq./L. range. A disturbance in the release of antidiuretic hormone probably was present. In the patient being discussed it is harder to be sure that simple dehydration was not present.

DR. ERIC REISS: Dr. Sherry, it may be worth pointing out that there are no physical findings referable to water depletion. Now, the findings of extracellular fluid depletion to the trained observer are quite typical, but water depletion is difficult to detect. Characteristically in water depletion the urine volume remains high for a long time despite the falling glomerular filtration rate. The apparent explanation for this

patient could be that the filtered salt load was extremely high. He was having a form of osmotic diuresis.

DR. SHERRY: My own view would be that the electrolyte disorder in this patient relates in part to the difficulty in fluid intake plus significant renal disease. The question remains as to whether or not there was an additional central factor. Dr. Bricker, would you consider for us the nature of the large abdominal mass, the azotemia, the hematuria and the mild hypertension which this patient portrayed?

DR. NEAL S. BRICKER: Given this constellation of symptoms and signs we have only one interpretation; that is that the patient did indeed have polycystic renal disease, that the berry aneurysm was associated with the polycystic disease and that we can explain the majority of the abnormalities on the basis of the underlying parenchymal disease of the kidneys and the rupture of the aneurysm.

DR. SHERRY: Do you believe that this patient was in uremia?

DR. BRICKER: At the time of admission he had significant nitrogen retention and although this may have been due in part to his catabolic state, his glomerular filtration rate undoubtedly was markedly depressed. There are several observations however, which indicate that he was not in advanced renal insufficiency, prior to his acute illness. These include a normal phosphorus value, and a calcium level which was also within the normal range. In addition, his hemoglobin concentration was so high that one may conclude, despite the presence of some degree of contraction of intravascular volume, that he was not anemic prior to the development of his present illness. For these reasons then I think that the degree of renal insufficiency he presented prior to his catastrophe was at most of moderate severity, and that a combination of events in his present illness resulted in the high values for non-protein nitrogen. These include the initial loss of functioning nephrons, a further decrease in filtration rate attendant upon volume contraction, and an additional elevation of urea levels due to the decrease in the volume of body water in which the urea is dissolved.

DR. SHERRY: Dr. Goldman, will you agree with this diagnosis of polycystic kidney disease or do you think we have to consider other types or renal disease seriously?

DR. MELVIN GOLDMAN: Some of the causes of hypertension in a young person should be considered. Most of them have been ruled out here. Coarctation of the aorta seems unlikely in that the femoral pulses were palpable. Of course, this does not completely rule it out. Adrenal cortical and adrenal medullary tumors must be considered in this situation. However most of these are quite far down on the list of possibilities.

DR. SHERRY: Dr. Bricker, do the cysts in patients with polycystic disease contribute significantly to renal function?

DR. BRICKER: In the adult patient with polycystic disease, having the onset of symptomatology after the third decade, there is good evidence that the cysts are connected dynamically with functioning nephrons. There undoubtedly is some contribution made by the cystic nephrons to the over-all functional capacity of the involved kidney. I think that it would be safe to conclude, however, that the majority of renal function is accomplished by nephrons which are either not cystic or have only small cysts.

DR. SHERRY: Are there any procedures, or particularly surgical procedures, which have any value in the treatment of polycystic disease?

DR. BRICKER: I think not, if the intent is to slow the rate of progression of renal insufficiency. The only indications for renal surgery in the patient with polycystic disease of the kidneys would appear to arise from complications such as massive hemorrhage or nephrolithiasis. The removal of one kidney, of course, in a patient with bilateral progressive disease must be performed with great trepidation.

DR. SHERRY: This patient had a unilateral mass. Does unilateral polycystic disease occur or or do you think that the mass felt on the right was the right kidney?

DR. BRICKER: Unilateral polycystic disease does occur. Postmortem series indicate that in approximately 8 per cent of the adult patients the disease is unilateral. However, there is every likelihood that if these patients were to have survived another ten years, the disease would ultimately have involved the contralateral organs. There is no information in the present case to allow us to establish with certainty the degree of involvement of the right kidney or the presence of cystic involvement of the liver.

DR. SHERRY: Is there any agreement about the pathogenesis of polycystic disease?

DR. BRICKER: I think that all the theories based on faulty union of embryologic anlage or upon persistence of their vestigial nephrons

must be abandoned in the light of physiologic evidence suggesting that the cysts are connected dynamically to functioning nephrons. There is no good theory to replace these but one might speculate that the cysts develop by virtue of weakening of the wall of the nephron and outpouching in an aneurysmal fashion.

DR. SHERRY: Several people have suggested that our case is an example of polycystic disease of the kidney occurring in association with a berry aneurysm which ruptured. Dr. Reiss, would you give us some information about this association.

DR. REISS: The association can be put in two ways. Among the people who have cerebral aneurysms it has been noted that roughly 4 per cent also have polycystic disease. Conversely, among the people who have polycystic disease roughly 17 per cent also have cerebral aneurysms. It might be mentioned in this connection, Dr. Sherry, that polycystic disease of the kidneys is not uncommonly associated with cysts elsewhere in the body, in bones, in the ovaries and in many other structures, and most prominently in the liver. This apparently is a common occurrence.

DR. SHERRY: Do you think our patient, if he had polycystic disease of the kidney, also had polycystic disease of the liver?

DR. REISS: This is a good statistical possibility.

DR. SHERRY: Is there any association of berry aneurysms with any other congenital abnormalities?

DR. REISS: Yes, berry aneurysms occasionally occur with other vascular abnormalities, such as aneurysms of the aorta and/or of the coronary arteries, rarely with dissecting aneurysms and coarctation.

DR. SHERRY: I was disturbed by the fact that this patient had hypertension described at the age of twenty-one. If he had polycystic disease of the kidney, it would be unlikely that he would have had hypertension at the age of twenty-one, Since the hypertension appears late in the course of polycystic disease. For this reason I wonder whether you thought there might be another congenital abnormality present, such as coarctation, which might have caused this early hypertension?

DR. REISS: I have considered this, but unfortunately the evidence is slim. There is one point in this connection, Dr. Sherry, that is worth mentioning. It is conceivable that the association of polycystic disease and ruptured cerebral aneurysm is due to the fact that the congenitally weakened muscular coat of the arteries is put under stress by the hypertension resulting from the advancement of the polycystic disease.

DR. SHERRY: The genetic factor in polycystic disease of the kidney is quite interesting. Dr. Alfred Goldman has studied a family with this disease and has made some genetic observations. I wonder if you might tell us about them?

DR. ALFRED GOLDMAN: The history of the family that I had an opportunity to study goes back five generations. Mr. X some hundred years ago married for the fourth time, and the polycystic disease can be attributed to his fourth wife. All the offspring from his previous marriages apparently remained free of the disease, according to the history obtained from members of the third generation. Mr. X had two male children both of whom died in middle age of "kidney disease." One of these had two boys, and the other had four boys and a girl. All of these died of proved congenital cystic disease at ages varying from forty-three to sixty-two years, except the girl who died in her early thirties following childbirth. There were four daughters born in the fourth generation, all of whom have cystic disease. One of those girls died recently at the age of thirty-nine. In the fifth generation, there are now six children, none of whom show clinical evidence of this disease at this time. However, special studies have not been made on them as yet.

DR. SHERRY: Polycystic disease then seems to be transmitted by a dominant gene; apparently not sex linked and with a very high degree of penetrance.

Dr. Lang, would you be willing to comment on the polycythemia that this patient presented? I noticed that it was mild, and it has been suggested that it was probably related to dehydration. Do you accept this or do you believe there are other factors which must be considered in this patient?

DR. R. LANG: I think that dehydration is the most likely explanation, however it would have been nice to have further data on the patient before his terminal event. There are possibilities of two different factors playing a role; one serving to depress his erythropoiesis and the other questionably related to increasing it. This combination may make for a normal level of hemoglobin concentration. It is well known that polycythemia has been associated with such

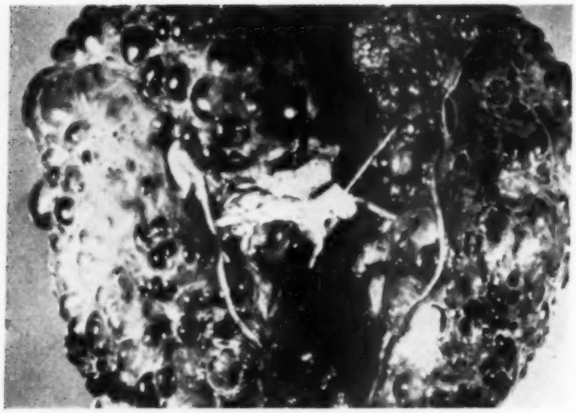


FIG. 1. Gross photograph of the surface of the kidneys. The kidneys weighed 3,000 gm. together and were composed of innumerable cysts of varying sizes.

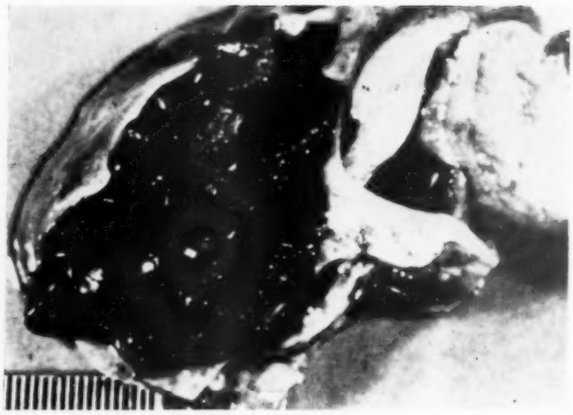


FIG. 2. Gross photograph of an opened cystic seminal vesicle containing amber translucent concrements of inspissated proteinacious material.

lesions as hypernephroma and polycystic disease of the kidney. It is also well known that the presence of uremia tends to decrease erythropoiesis. Perhaps these two mechanisms were balancing each other out.

DR. SHERRY: In summary, I believe this patient had a cerebral aneurysm, probably of the left cerebral artery which ruptured into the brain, and which was associated with polycystic kidney disease. The hypernatremia and hyperchloremia may be explained by a combination of dehydration, renal and perhaps hypothalmic factors. There is the possibility that the patient may also demonstrate some atelectasis and hypostatic pneumonia as a terminal event. Dr. Kissane will present the pathology.

PATHOLOGIC DISCUSSION

DR. JOHN M. KISSANE: Aside from an enlarged heart which weighed 550 gm., rather marked patchy pulmonary atelectasis and acute and chronic passive congestion of the liver and spleen, the major abnormalities at autopsy were confined to the urinary tract and the central nervous system. The kidneys (Fig. 1) were both enormously enlarged, weighing 3,000 gm. together. The renal parenchyma was composed of innumerable cysts ranging from barely visible to 4 cm. in diameter. The pelves of both kidneys were moderately dilated; the ureters were normal. Both seminal vesicles presented a peculiar appearance (Fig. 2) as large cystic sacs containing concrements of inspissated proteinacious material. The cut surface of the kidneys showed the extent of the cystic alteration. (Fig. 3.) There were only small patches of relatively normal parenchyma in the two kidneys. In the brain, there was a massive intracerebral hemorrhage on the left side which had destroyed the left basal ganglia and thalamus and involved the internal capsule. The left aspect of the hypothalamus was involved in the area of hemorrhage and contiguous softening. The right side of the hypothalamus and the pituitary were normal. The cerebral vessels showed slight arteriosclerosis; no aneurysm was found. On microscopic examination the cysts in the kidneys were of varying sorts. A search of several slides revealed a few cysts in which relatively normal glomeruli could be identified. (Fig. 4.) The finding of normal and nearly normal glomeruli in the cysts of persons with polycystic disease of the kidneys has been taken as evidence against the non-union theory of the genesis of that disease since the glomerulus and the first portions of the nephron will not differentiate when union of the ureteral bud and the tissue of the nephrogenic ridge is prevented experimentally. Another common finding in kidneys of this sort is papillary excrescences of tubular type epithelium extending into some of the cysts. The presence of these papillary proliferations led some older writers to consider polycystic kidneys as benign neoplasms, analogous to cystadenoma of the ovary. Another type of epithelium which lines some cysts is composed of tall pyramidal cells bulging into the lumen, and with basal hyperchromatic nuclei closely mimicking the lining of the proximal tubule, even to the presence of a fragmented but recognizable brush border. The most abundant type of epithelium in this kidney is composed of cuboidal cells with central

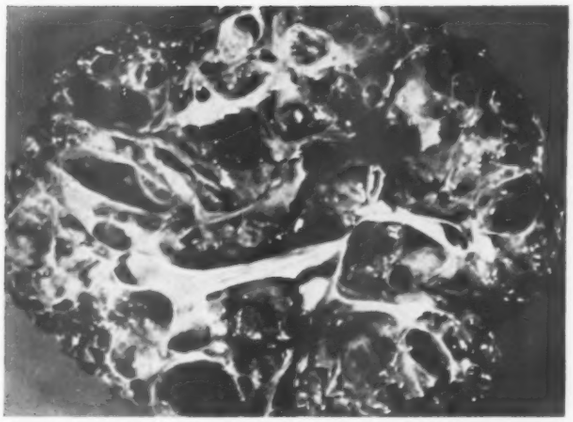


FIG. 3. Cut surface of the left kidney showing virtually complete replacement of parenchyma by cysts.

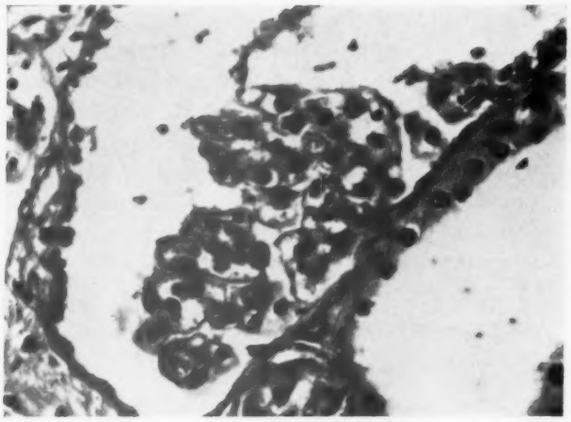


FIG. 4. Photomicrograph of kidney; hematoxylin and eosin, magnification × 170. One of the small cysts contains a well formed glomerulus extending into the lumen.

vesicular nuclei, and resembles the lining of the collecting tubules. Serial reconstructions of the cysts in polycystic disease have, in fact, disclosed that the cysts can arise from any portion of the nephron. This is taken as evidence against both the non-union hypothesis and the delayed-involution hypothesis of the genesis of polycystic disease. In the architecturally more normal parenchyma in this kidney were areas of interstitial fibrosis, tubular atrophy, rather dense inflammatory infiltrate and glomeruli surrounded by pericapsular fibrosis, recognizable as chronic pyelonephritis. Cortical arterioles were greatly thickened and contained globules of eosinophilic hyaline material in the media. (Fig. 5.) The concomitance of acquired renal disease, such as pyelonephritis and vascular disease, in adult patients with polycystic disease is a regular occurrence and is used to explain the bimodal age distribution of autopsy series. If an individual has enough uninvolved parenchyma to survive the first weeks or months of life, the relatively great propensity of the kidney for hypertrophy in the newborn is thought to provide adequate functional parenchyma until degenerative renal diseases, such as pyelonephritis and vascular disease, tip the balance by damage to the marginal amount of functioning parenchyma. In sections of the cystic seminal vesicles the papillary appearance of the seminal vescicle is well preserved. Cysts of seminal vesicles are extremely rare. They are usually thought to be congenital, and I know of no reported instances associated with polycystic kidneys. The association of cysts in the liver, pancreas, spleen or other organs was not present in this case. Microsections of the left internal capsule of the brain showed massive destruction by hemorrhage fully consistent with the two or three weeks' duration. In the myocardium there were, in addition to old areas of interstitial fibrosis, fairly numerous zones of recent destruction of myocardium where the replacement by fibrous tissue was incomplete. This would be consistent with a duration of about two to three weeks. Although the degree of coronary arteriosclerosis was only slight, these areas had the anatomic appearance of ischemic myocytolysis.

DR. SHERRY: No berry aneurysm was demonstrated?

DR. KISSANE: The association of cerebral aneurysms with polycystic kidney was in everyone's mind when we examined this brain, yet we found none, and as far as we can ascertain this is just a simple hemorrhage on a hypertensive basis. The hemorrhage was primarily intra-

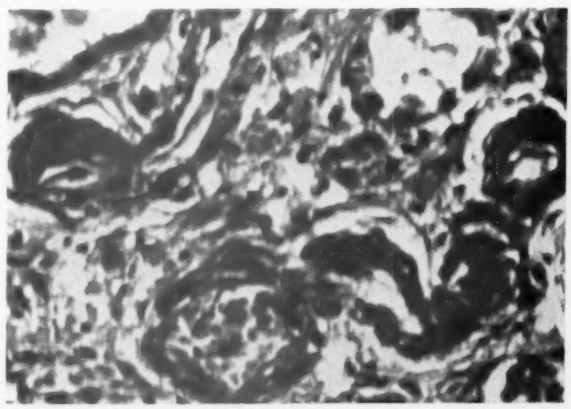


FIG. 5. Photomicrograph of kidney; hematoxylin and eosin, magnification × 360. A group of cortical arterioles with thickened, focally hyalinized walls.

cerebral rather than subarachnoidal. It is said that 22 to 25 per cent of the patients with polycystic disease die of intracranial hemorrhage, about 18 per cent from demonstrable aneurysms; so this patient falls into the small group who die of other types of cerebral hemorrhage.

The final anatomic diagnoses are polycystic disease; hydronephrosis, bilateral, moderate; chronic pyelonephritis, bilateral, moderate; arterial and arteriolar nephrosclerosis, moderate; arteriolar sclerosis in the adrenals, pancreas, and liver, moderate; cystic seminal vesicles, bilateral; hypertrophy of the heart, 550 gm.; focal fibrosis in the myocardium; partially healed micro infarcts in the left ventricle; intracerebral hemorrhage in the left hemisphere communicating with the left lateral ventricle.

Case Reports

Hemoglobin S-C Disease with Fat Embolism*

Report of a Patient Dying in Crisis; Autopsy Findings

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HEMOGLOBIN C, identified in 1950 by Itano and Neel [*1*], is inherited as a simple Mendelian dominant character, allelic with the genes for hemoglobin A, hemoglobin S and other abnormal hemoglobins, but not allelic with the genes for elliptocytosis, spherocytosis or thalassemia. Hemoglobin C participates in the following hematologic syndromes:

Hemoglobin C Trait. This is a heterozygous state in which the individual inherits hemoglobin C from one parent and hemoglobin A from the other. Carriers are usually asymptomatic except for intermittent arthralgia. Anemia is not significant, and hematologic abnormalities include mild and variable degrees of leptocytosis (0 to 40 per cent), reticulocytosis, and decreased osmotic fragility. Electrophoresis demonstrates a hemoglobin A + C pattern, hemoglobin C being present in amounts ranging from 25 to 40 per cent.

Homozygous Hemoglobin C Disease. This state is characterized by a compensated hemolytic process or a mild anemia. Marked leptocytosis (50 to 70 per cent), reticulocytosis and decreased osmotic fragility are more severe in this disease than in the sickle cell trait. Electrophoresis reveals hemoglobin C in amounts ranging from 85 to 100 per cent, the remainder being hemoglobin F. Splenomegaly is almost always present, both in children and adults, and may be pronounced. Episodic bone and joint pain occasionally occurs but full-blown crises have not been reported. Splenectomy [*2–5*] does not appear to influence the condition.

Other Heterozygous Hemoglobin C Syndromes. Several of these have been observed and other theoretically possible combinations remain to be found clinically. Avery [*6*] has described two cases of hereditary elliptocytosis and hemoglobin C, an essentially innocuous condition in which the abnormal shape of the erythrocytes is inherited from one parent and the abnormal hemoglobin is inherited from the other. Smith and Conley [*7*] cite an example of hemoglobin C-spherocytosis with clinical remission following splenectomy. Several cases of hemoglobin C-thalassemia have been described [*8–11*]. This syndrome is characterized by a microcytic hypochromic anemia, and the usual leptocytosis, reticulocytosis and abnormal osmotic fragility. The electrophoretic pattern is usually C + F + A. Splenomegaly is not invariably present. The anemia tends to be chronic and moderately severe, but crises are infrequently observed. Several cases of hemoglobin S-C disease (sickle cell-C disease) have also been described [*7,12–16*]. The anemia is normochromic and normocytic. Leptocytosis, reticulocytosis and decreased osmotic fragility are prominent. Tests for sickling are positive. The electrophoretic pattern frequently shows approximately equal quantities of hemoglobin C and hemoglobin S, but hemoglobin C may vary from 35 to 63 per cent and hemoglobin S from 37 to 65 per cent. Splenomegaly has been observed in most cases, but shrunken spleens weighing less than 40 gm. were described at autopsy in two patients dying of postpartum hemorrhage [*17*]. A variety of clinical manifestations have been reported in hemoglobin S-C disease, all essentially similar to those seen in sickle cell anemia (S-S disease), but they are apt to be milder, more variable in frequency, with onset later in life; these include osteoarticular crises, abdominal crises and subarachnoid bleeding. Crises during pregnancy, aseptic necrosis of the femoral head, pulmonary infarctions, splenic infarction following airplane

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travel, and hematuria are encountered more frequently in S-C disease than in S-S disease.

Heterozygous hemoglobinopathies rarely are the cause of death. Berthrong et al. [*18*] have reported an autopsy case of hemoglobin S-thalassemia in a forty-two year old man of Greek descent in whom the fatal crisis was precipitated by an airplane trip. Green et al. [*17*] have described three patients with hemoglobin S-C disease in whom severe hemolytic crises developed during pregnancy; two died of postpartum hemorrhage and were autopsied; the third died at home. Jensen et al. [*19*] have reported the case of a fifty-two year old Negro with homozygous hemoglobin C disease who died of multiple repeated pulmonary infarctions. Wade and Stevenson [*20*] have reported the case of a forty-nine year old Greek woman with "sickle cell anemia" who died with disseminated fat embolism following acute crisis; in retrospect, the patient's ethnic origin, onset of symptoms in adult life, age at death, presence of normoblasts in the peripheral blood, and enlarged spleen suggest that this may be an example of sickle cell-thalassemia. Vance and Fisher [*21*] likewise reported the case of a forty-nine year old Negro woman who died in crisis with intravascular sickling and fat embolism; again, the clinical and hematologic features suggest one of the heterozygous conditions, probably hemoglobin S-C disease. Wertham, Mitchell and Angrist [*22*] reported several cases of sickle cell anemia with cerebral manifestations, one in a twenty-eight year old Negro woman in whom crisis developed following a respiratory infection. Autopsy showed multiple cerebral capillary thromboses with encephalomalacia, multiple pulmonary thromboses with infarction, fat emboli to the brain, lungs and glomeruli, and extensive sickling in the marrow sinusoids. In view of the fact that prior to her terminal illness the patient had been in good health except for migratory polyarthritis for five years, it is tempting to reclassify this as a probable case of S-C disease. Diggs and Jones [*23*] reported a fatal case of probable S-C disease in a forty-eight year old Negro woman who had severe pain in the back and lower extremities, drowsiness and stupor. Tests for sickling were positive and the peripheral blood contained numerous target cells. Fat embolism was not a prominent feature, but extensive intravascular sickling was noted in many tissues at necropsy. However, Wyatt and Orrahood [*24*] reported a fatal case of probable S-C disease in a twenty-eight year old Negro woman, thirty-seven to thirty-eight weeks pregnant, with similar symptoms. Autopsy disclosed hemorrhagic infarction of the bone marrow, fat embolism to lung, kidney and brain, and intravascular sickling in the marrow sinusoids and pulmonary vessels. These cases [*17*–24] were studied prior to the development of hemoglobin electrophoresis.

More recently Eastman [*25*] has presented clinical details and a pathologic summary of a case of hemoglobin S-C disease, confirmed by electrophoresis, in a forty year old Negro woman who died in crisis at thirty-eight weeks of gestation with infarctive necrosis of the bone marrow, embolization of fat and marrow to the lungs, and fat embolism in the brain and glomeruli. Edington [*26*] has reported necropsy findings in three young Ghanese primipara who died suddenly at fourteen, thirty and thirty weeks of gestation. The diagnosis of hemoglobin S-C disease was established by electrophoresis. In all three cases there was splenomegaly, and both the liver and spleen showed diffuse intrasinusoidal sickling. Siderofibrotic nodules were not seen in the spleens, although iron pigment was identified in the cells lining the sinusoids and in the capsule. The pulmonary capillaries were packed with agglutinated masses of erythrocytes; intra-alveolar edema fluid was present and a small pulmonary infarct was found in one case. Edington also noted briefly the autopsy findings in two Ghanese males dying suddenly with infections complicating hemoglobin S-C disease. In both cases the spleens were enlarged and exhibited siderofibrotic nodules. Extensive intravascular sickling was prominent.

The case reported here is one of hemoglobin S-C disease with death in acute crisis. The events precipitating the crisis remain obscure, but postmortem examination suggests a sequence of events which may be common to fatal cases of hereditary hemoglobinopathies.

CASE REPORT

C. G., a twenty-eight year old Negro male window washer, was admitted to Knickerbocker Hospital in coma. He had been in excellent health with no previous history of anemia, osteoarticular pain or previous hospitalization. Six months before he had had an episode of pleuritic pain. A roentgenogram of the chest at that time revealed evidence of a small, ill defined, homogeneous shadow at the left base just above the diaphragm. This was interpreted as a patch of pneumonia or infarction of the involved lung.

His present illness began three days prior to admission when he experienced the sudden onset of low back pain while washing windows. He attributed this to having strained his muscles while at work. He was seen in the Emergency Ward of Knickerbocker Hospital on the following day and treated with salicylates and back strapping. This did not relieve his symptoms and he returned to the Emergency Ward the next day complaining of more severe lumbosacral pain. A roentgenogram of his lumbodorsal spine showed no abnormalities; he was given Demerol® 100 mg. and referred to the Surgical Clinic the next day.

However, that evening he had a fever with temperatures of 100° to 101.6°F.; he complained of severe headache, and became delirious. Late that night he lapsed into a stupor from which he could be aroused only for brief intervals. On the morning of admission he was in coma, responding only to painful stimuli. Prior to this illness he had not been regularly employed. He was described as a "moderate week-end drinker," never consuming more than a pint of whiskey a week. Narcotic addiction was denied. Exposure to sewage, contaminated water or noxious chemicals such as carbon tetrachloride was also denied.

Physical examination revealed an acutely ill, comatose, well developed, robust young Negro man responding only by groans to painful stimuli. There was evident, although moderate, respiratory distress. The temperature was 100.4°F.; pulse, 132; respiration, 28; blood pressure, 130/80 mm. Hg. Random movements of the eyes were present. The pupils reacted to light and corneal reflexes were elicited. There was questionable scleral icterus. Funduscopic examination revealed normal optic discs and vessels; there was no papilledema. The teeth were clenched, and the gums were hypertrophied. Several small bleeding points were present in the buccal mucous membranes. The neck was stiff. The trachea was in the midline and the thyroid gland was not palpable. The cervical lymph nodes were not enlarged. Examination of the heart revealed the point of maximal impulse to be in the fifth intercostal space in the mid-clavicular line. The rhythm was rapid and regular without dropped beats. The aortic second sound was louder than the pulmonic second sound. There was no murmur or gallop. The lungs were clear to percussion and auscultation. The abdomen was slightly tense and diffusely tender. The inferior border of the liver was felt 3 cm. below the right costal margin. The spleen was not felt. Active peristaltic sounds were heard. No masses were encountered on rectal examination and the prostate was of normal size. No petechiae or ecchymoses were noted. Neurologic examination revealed no paralysis, normal plantar reflexes, absent superficial reflexes, absent deep tendon reflexes in the lower extremities, and questionable decrease of tendon reflexes in the right arm.

Laboratory studies showed a hemoglobin of 11.3 gm. per cent; red cell count, 3.6 million per cu. mm.; mean corpuscular hemoglobin 31 μg.; white cell count, 8,500 per cu. mm. (corrected) with 60 per cent neutrophils (including 18 per cent stab forms, 12 per cent juvenile forms and 10 per cent metamyelocytes), 36 per cent lymphocytes, 1 per cent eosinophils and 3 per cent monocytes. There were 65 normoblasts per 100 white blood cells. The reticulocyte count was 0.2 per cent. About half of the erythrocytes were well shaped and adequately hemoglobinated, but about half were in the form of target cells. (Fig. 1.) The platelet count was 92,000. A sickle cell preparation was positive, about 90 to 95 per cent of the red cells being sickled. A smear of sternal marrow showed markedly increased cellularity with pronounced normoblastic hyperplasia. (Fig. 2.)

The urine had a specific gravity of 1.012, was free of sugar and acetone, but showed 4 plus protein. The sediment contained 10 to 24 red blood cells and 4 to 12 white blood cells per high power field. Hyaline and granular casts were abundant. Urine cultures yielded B. proteus, B. pyocyaneus and hemolytic streptococci. Blood cultures were sterile.

An immediate spinal tap was performed. The fluid was under an initial pressure of 210 mm. of water; the final pressure was 150 mm. after 10 ml. were withdrawn. The fluid was crystal clear, contained 2 lymphocytes per cu. mm., 46 mg. protein, 79 mg. glucose, 710 mg. chloride, and was sterile.

The bleeding time was two hours and four minutes. The clotting time was three hours and twenty minutes. Direct and indirect Coombs' tests were negative. The serum carbon dioxide was 21 mM/L. The bromsulfalein test showed 64.5 per cent retention of dye at thirty minutes. The serum non-protein nitrogen was 64 mg. and the creatinine was 2.85 mg. The serum bilirubin was 2.25 mg. total, with 1.25 mg. indirect and 1.00 direct. The cephalin flocculation reaction was 3 plus. The total protein was 6.0 gm. per cent with 3.3 gm. albumin and 2.7 gm. globulin. The serum cholesterol was 223 mg. per cent, 180 mg. were esterified. The prothrombin time was eighteen seconds (control thirteen seconds). The serum glutamic-oxaloacetic transaminase was 114 units.

An electrocardiogram showed a normal sinus rhythm with a ventricular response of 150 per minute. U waves were prominent throughout the tracing. The S-T segments in leads II, III, aVf, V_4, V_5 and V_6 were depressed and flattened. A "staircase-like" configuration of the S-T segments was present in the standard leads. There was an R-S-R′ complex in aVr. The tracing was interpreted as showing incomplete right bundle branch block. The prominent U waves and alteration in S-T segments were considered consistent with acute pulmonary hypertension.

The patient was treated with the administration of intravenous fluids, and a gastric tube was passed for feeding. Fluid aspirated from the stomach contained

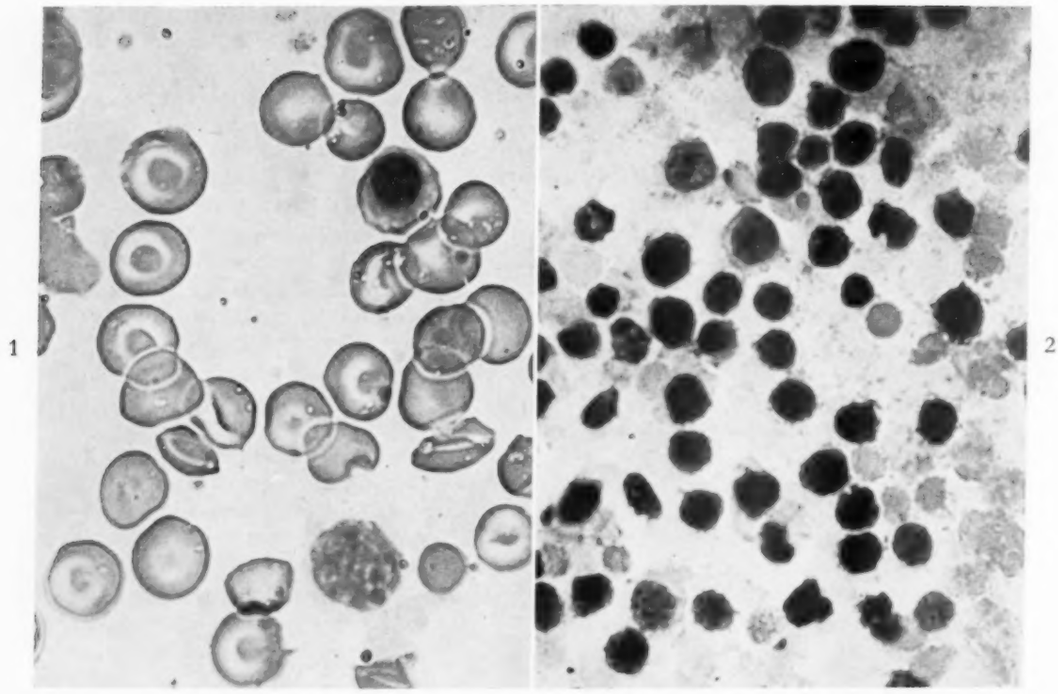


FIG. 1. Smear of peripheral blood showing a normoblast and several target cells, one partially sickled.

FIG. 2. Bone marrow aspiration showing increase in normoblasts and other erythropoietic elements.

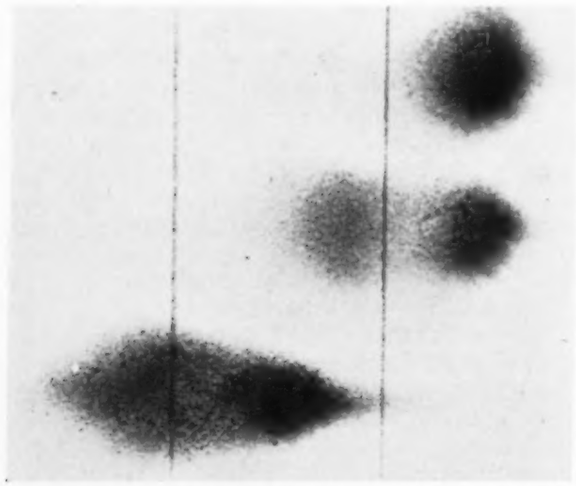


FIG. 3. Hemoglobin electrophoresis. The upper line shows a normal control (hemoglobin A); the second line shows the patient's mother (hemoglobin A + hemoglobin S); the third line shows the patient (hemoglobin S + hemoglobin C).

reddish brown material resembling recently acidified blood. Consequently, Wangensteen suction was instituted. Approximately 450 cc. of bloody fluid was aspirated over the next twenty hours. Six hours after admission the temperature spiked to 105.6°F. Treatment with aspirin suppositories and alcohol sponges reduced the temperature to 103.6°F. where it remained thereafter. Coma persisted and the general condition of the patient deteriorated. Respiratory distress increased although auscultation of the chest continued to reveal little.

Sixteen hours after admission the hemoglobin had fallen to 8.5 gm. per cent; the red cell count was 2.6 million per cu. mm.; and the mean corpuscular hemoglobin was 33 μg. The white cell count was 7,330 per cu. mm. with essentially an unchanged differential count. The platelet count was 82,000 per cu. mm. The reticulocyte count was 0.3 per cent. The urinary output for twenty-four hours was 1,200 cc.

The morning after admission he passed some loose black stools. Before transfusions could be started he died suddenly, twenty-six hours after admission. After death, blood taken for agglutination tests for Weil's disease was reported negative. Blood drawn for hemoglobin electrophoresis showed 38 per cent hemoglobin C and 62 per cent hemoglobin S. Alkali denaturation failed to show any hemoglobin F. (Fig. 3.)

The prosection was performed by Dr. Dominick DiMaio of the Office of the Chief Medical Examiner of New York City. The heart weighed 400 gm. The left ventricle was hypertrophied, measuring 15 mm. in thickness, and the right ventricle was dilated and flabby. There were no lesions on the valves, endocardial surfaces or in the myocardium. Microscopically, no lesions were seen. The lungs had a combined weight of 1,000 gm. There were numerous petechial hemorrhages on the visceral pleura. The lungs were subcrepitant and moderately heavy. No grossly

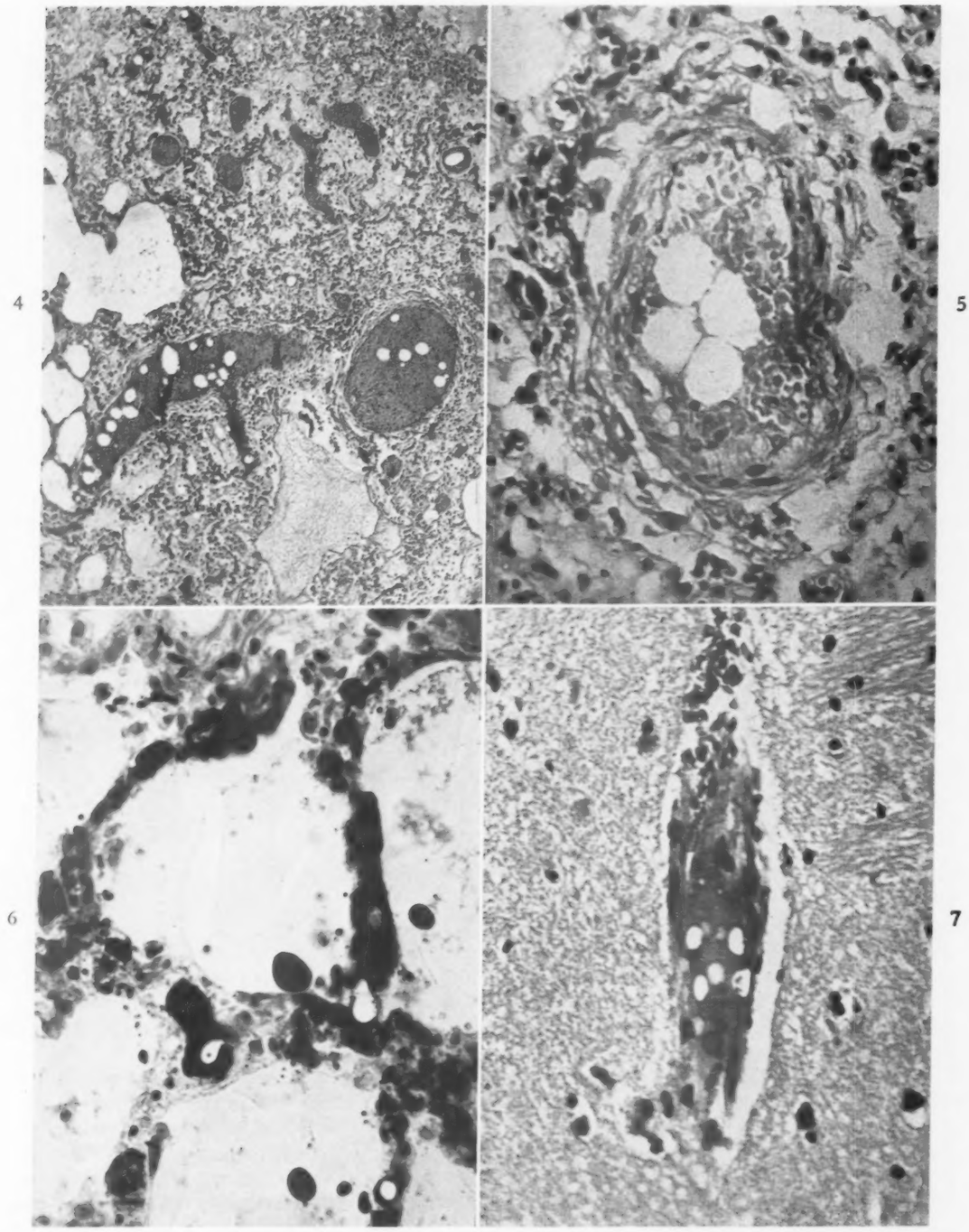


FIG. 4. Lung showing congestion of medium and small arteries as well as capillaries by conglutinated erythrocytes. Lipid vacuoles are admixed with the thrombi. Intra-alveolar edema fluid is present.

FIG. 5. Lung. A medium-sized artery contains embolic fat cells and sickled erythrocytes.

FIG. 6. Lung stained with Sudan black B. Lipid globules fill alveolar capillaries.

FIG. 7. Brain showing a small blood vessel in which vacuoles of lipid are present.

visible thrombi or emboli were seen on dissection of the arterial tree. The cut surfaces were bright red with scattered linear streaks and had a granular moist texture, but there were no areas of consolidation or infarction. Microscopic examination showed diffuse congestion of the medium and small arteries as well

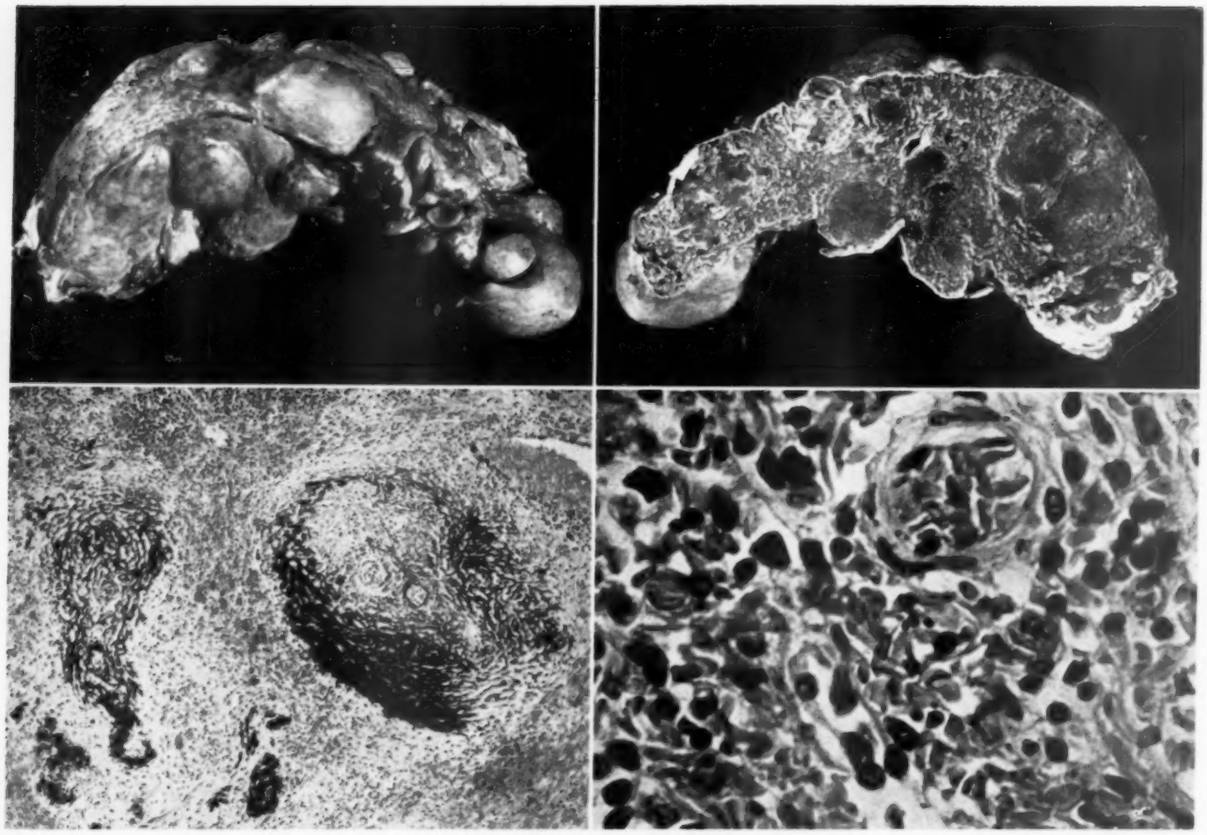


FIG. 8. Spleen weighing 70 gm. showing projecting bosselations and depressed scars, capsular surface (*upper left*).

FIG. 9. Cut surface of spleen showing congestion of bosselated areas and fibrous scarring of retracted areas (*upper right*).

FIG. 10. Spleen showing a peri-arteriolar siderofibrotic nodule (*lower left*).

FIG. 11. Spleen showing intrasinusoidal sickling of erythrocytes. Irreversibly sickled cells and sickled normoblasts are present (*lower right*).

as of the capillaries in the alveolar walls. (Fig. 4.) In many areas there was extensive intravascular sickling of erythrocytes with the formation of innumerable conglutinative thrombi. Delicate strands and occasional aggregates of fibrin were present in association with many of the larger thrombi, indicating their formation antemortem. Many of the red cell aggregates contained clear vacuoles with sharp margins, some preserving the contour of fat cells. (Fig. 5.) Similar vacuoles were seen distending alveolar capillaries. Sections stained with Sudan black B showed these intravascular globules to be lipid. (Fig. 6.) It was in association with these finely divided globules of lipid that intravascular sickling and conglutinative thrombosis were most prominent. Megakaryocytes were prominent in the pulmonary capillaries. There was also a patchy distribution of intra-alveolar edema fluid and a small amount of fibrin.

The brain weighed 1,320 gm. On gross examination there was no evidence of hemorrhage or exudate. Microscopic examination showed patchy congestion of many cerebral small arteries and capillaries by sickled erythrocytes. In a few small arteries clear vacuoles were admixed with the conglutinated thrombi. (Fig. 7.) These vacuoles as well as less easily visible globules within the capillaries stained positively for lipid with Sudan black B. Areas of softening and necrosis were not present in the brain.

The spleen weighed 70 gm., had a shrunken, coarsely nodular contour and a smooth dusky violet surface. (Fig. 8.) On section, the depressed areas were greyish retracted scars, and the bosselations were firm congested red pulp. (Fig. 9.) The Malpighian corpuscles were not grossly visible. Microscopic examination showed broad zones of irregular dense hyaline scarring of the parenchyma, frequently with evidence of remote arterial and arteriolar thrombosis. A delicate lattice-work of fibrillary material upon which blackish granular material was deposited served to outline the adventitia of many small arteries and arterioles. (Fig. 10.) These were prominent in scarred areas, particularly near the margin between zones of old infarction and acute congestion, forming typical

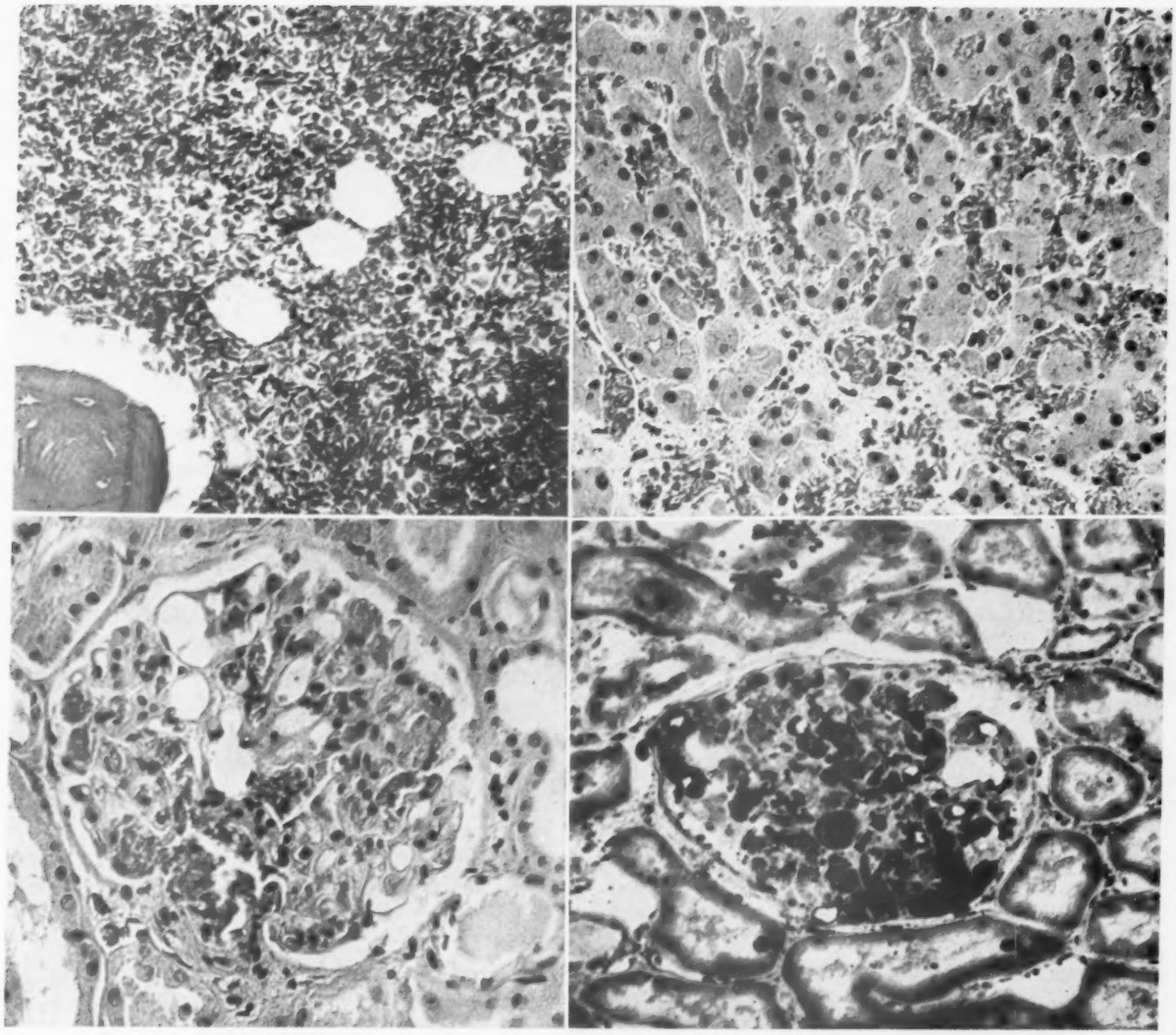


FIG. 12. Bone marrow showing a hyperplastic marrow overrun by sickled erythrocytes (*upper left*).

FIG. 13. Liver showing intrasinusoidal sickling (*upper right*).

FIG. 14. Kidney showing a glomerulus, some loops containing sickled erythrocytes, others distended by embolic fat (*lower left*).

FIG. 15. Kidney stained with Sudan black B. The embolic lipid is stained deep black. A few droplets are found within tubular lumens (*lower right*).

siderofibrotic nodules (Gamna-Gandy bodies). Most of the remaining red pulp showed sinusoidal congestion with diffuse intrasinusoidal sickling of erythrocytes. (Fig. 11.) Sickling of normoblasts was also observed. Iron pigment was identified in endothelial cells lining sinusoids. The Malpighian corpuscles were reduced in number and size, inactive, consisting only of a moderate aggregation of lymphocytes eccentrically dispersed about an arteriole.

The bone marrow was dark red and very cellular. Microscopic study showed extensive areas of acute hemorrhagic infarction, the sinusoids being stuffed with sickled erythrocytes which overran the myeloid and adipose elements of the marrow. (Fig. 12.) Many of the sickled cells were in the long filamentous form indicative of irreversible sickling. The osseous tissue itself was not infarcted in the areas examined, and there was no older necrosis of the marrow. In a few spared areas the marrow was hypercellular with preponderance of erythropoietic elements.

The gastrointestinal tract contained small amounts of reddish material in the upper portion (stomach and small intestine) and blackish material in the large intestine. No definite bleeding point was identified. The liver weighed 2,400 gm., had a smooth dark reddish brown surface and a uniformly red-brown cut surface which appeared congested with indistinct lobular markings. Microscopic examination showed

a pronounced degree of sinusoidal congestion which was generalized and not restricted to any particular zone of the lobules. Sickled erythrocytes in small clumps were seen in many sinusoids, but there was no evidence of phagocytosis by von Kupffer cells, nor any evidence of fatty metamorphosis of the parenchymal cells. (Fig. 13.) There was no inflammatory infiltrate, fibrosis or necrosis. The gallbladder and ducts were free of calculi and patent. The pancreas appeared normal on both gross and microscopic examination.

Grossly and microscopically the adrenal glands showed no significant lesions other than a few intrasinusoidal conglutinations of sickled erythrocytes. The kidneys weighed 180 gm. each, had smooth capsular surfaces, and on section the parenchyma bulged slightly above the divided capsule. The corticomedullary architecture was normal, and the glomeruli were visible as prominent bright red dots. Microscopic examination showed small conglutinations of sickled erythrocytes in loops of the glomerular tuft. In almost every glomerulus one or more of the peripheral loops were distended by a clear, sharply marginated vacuole which stained positively for lipid with Sudan black B. (Figs. 14 and 15.) Occasional tiny droplets of sudanophilic material were seen in tubular lumens, often in close apposition to tubular epithelial cells. There was no evidence of acute or chronic inflammation in the kidneys.

Family Study. Unfortunately, the patient had no siblings and no children. His father had deserted him shortly after he was born and could not be located. Only the patient's mother was available for study. She is a forty-eight year old Negro woman, essentially in good health except for intermittent joint pains which have recurred in mild form over the past eight to ten years, well developed and well nourished. There is no splenomegaly or hepatomegaly. Her hemoglobin is 13 gm. per cent; red cell count, 4.58 million per cu. mm.; hematocrit, 40 per cent; white cell count, 4,600 per cu. mm. with 58 per cent neutrophils, 39 per cent lymphocytes and 3 per cent eosinophils. The reticulocyte count is 1.8 per cent. Only a few target cells are present in the smear of peripheral blood. The osmotic fragility is 0.38 to 0.28, (control 0.42 to 0.34). A sickle cell preparation is positive, 85 to 90 per cent of the cells being sickled. Hemoglobin electrophoresis revealed 54 per cent hemoglobin A and 46 per cent hemoglobin S; no hemoglobin F was demonstrable.

The patient's mother thus has sickle cell trait; it is inferred that he inherited the gene for hemoglobin S from her and the gene for hemoglobin C from his father.

COMMENTS

Shortly after admission it was evident that the patient presented either an uncommon disease or else a common disease with most bizarre manifestations. The brief, non-specific prodrome of low back pain which became progressively more severe was followed by the rapid onset of coma with signs, symptoms and laboratory observations indicating involvement of the central nervous system, hematopoietic system, kidneys and lower urinary tract, liver and cardiopulmonic circulation. These were consistent with a wide variety of systemic diseases, infections and infestations, ranging from polyarteritis to bacterial endocarditis with diffuse embolization to leptospirosis. Of particular value in establishing the underlying hematologic disorder were the findings in a robust young Negro, without history of previous anemia or osteoarticular crisis, the presence of a positive test for sickling, a large number of target cells in the peripheral smear, and a pronounced normoblastic response in the face of a normocytic, normochromic anemia. The absence of splenomegaly was consistent with a chronic "sickling state," and the patient's ethnic origin, age at onset of illness, and leptocytosis suggested the presence of hemoglobin C. The laboratory diagnosis of hemoglobin S-C disease was confirmed after death when the hemoglobin electrophoresis was reported.

The anatomic observations aid in the interpretation of some of the clinical phenomena and laboratory data. Respiratory distress, tachycardia disproportionate to temperature, and the electrocardiographic changes are explained by pulmonary hypertension secondary to the diffuse antemortem conglutinative thrombosis which obstructed the pulmonary arterial bed and produced acute cor pulmonale. The dilated, flabby right ventricle is consistent with this diagnosis. Moser and Shea [27] have described pulmonary infarction, often multiple and progressive, with the development of chronic cor pulmonale in sickle cell anemia, sickle cell-thalassemia and hemoglobin S-C disease. It is apparent from the present case that acute cor pulmonale may develop in such patients as well; although no overt infarction was present, the extensive thromboses were sufficient to increase pressure in the lesser circulation. In retrospect, it appears probable that the episode of pleuritic pain and radiographic changes six months previ-

ously represented a small pulmonary infarction.

The hepatomegaly and increased retention of bromsulfalein are explained perhaps by obstruction of the hepatic sinusoids, the clearance of bromsulfalein being dependent upon the integrity of the hepatic circulation even though the parenchymal cells show no evidence of structural damage. The lesions in the liver were acute, entirely the effect of intrasinusoidal sickling. None of the chronic hepatic lesions described by Green et al. [*17*] or Song [*28*] were seen. Likewise, azotemia and the pronounced proteinuria can be ascribed to the obstruction of glomerular loops by embolic fat as well as by the conglutinated erythrocytes. The coma and other signs of diffuse involvement of the central nervous system are equally well explained on the basis of cerebral fat embolism and intravascular sickling. Failure to find an anatomic bleeding point for the clinically evident gastrointestinal hemorrhage is interpreted as indicating that the hemorrhage was capillary in origin, possibly secondary to sickling in terminal capillary loops in the mucosa, certainly diffuse in nature.

The hematologic observations revealed that 90 to 95 per cent of the red cells sickled, that about 50 per cent were in the form of target cells, and that the electrophoretic pattern was S + C. Sickling in various stages was seen in target cells. The liberation of normoblasts into the peripheral blood is not uncommonly found in crises of sickle cell disease and its genetic variants. However, it is evident that this particular crisis may not have been conspicuously "hemolytic" in origin. The serum bilirubin of 2.25 mg. three days after the onset of symptoms is scarcely impressive evidence that intravascular hemolysis initiated the sequence of events. The patient entered the crisis with a "compensated" bone marrow, i.e., the decreased erythrocyte survival time was balanced by hyperplasia and hypertrophy of the marrow. Whether or not such a marrow is more vulnerable to insult by intrasinusoidal sickling is speculative. However, if the prodrome of low back pain can be equated with the onset of infarction of vertebral marrow, the subsequent course is explained on the basis of fat embolization to the lungs, brain and kidneys from the marrow. This would imply that the acute hemorrhagic infarction (stuffing) of myeloid substance with sickled cells, many in filamentous form, disrupted the architecture of the marrow and mechanically displaced fat from ruptured fat cells as well as intact fat cells into sinusoids from whence they were hematogenously dispersed. Krevans [*29*] has observed megakaryocytes in peripheral blood and marrow emboli in pulmonary vessels in patients with hemoglobin S-C disease dying in crisis. The finding of formed fat cells and megakaryocytes in the pulmonary vessels in this case coincides with this observation. We are tempted to explain the normoblasts and metamyelocytes in the peripheral blood as the sequel of marrow infarction with extrusion of these cells along with the fat. The low reticulocyte counts reflect the infarction of the marrow and its failure after insult to release erythrocyte precursors in an orderly fashion. There is no morphologic evidence in the areas of spared marrow to indicate that the crisis was "aplastic" or "aregenerative." The crisis was the result of intravascular sickling.

Intravascular sickling is an effect of deoxygenation. Speculation outruns evidence in an effort to explain the nature of the initial insult to the bone marrow. Insofar as information from the family of a comatose patient permits, exposure to known marrow toxins, to high altitudes or decreased atmospheric pressures have been eliminated. The role of bacilluria remains ambiguous; there was neither bacteremia nor evidence of acute or chronic renal infection: whether or not an acute infection of the lower urinary tract precipitated the sequence of events cannot be determined. However, it is known that patients with sickle states are more susceptible to urinary tract infections. Some support for the notion that infection can precipitate intravascular sickling is found in the two cases of hemoglobin S-C disease noted briefly by Edington [*26*] and the case reported by Wertham, Mitchell and Angrist [*22*].

Griggs and Harris [*30*] have demonstrated the intermediate position of the blood in hemoglobin S-C disease and hemoglobin S-thalassemia in respect to tactoid formation, gelation, increase in the per cent of sickled cells, increase in blood viscosity, and increase in mechanical fragility when compared with the blood in sickle cell anemia and sickle cell trait under progressively reduced oxygen tensions. Although intravascular sickling can occur under physiologic conditions in patients with pure hemoglobin S, it is unlikely that this occurs in large measure in patients with a mixture of hemoglobin S and hemoglobin C. Support for this hypothesis is found in the observation that splenic infarction can occur spontaneously in patients with sickle

cell anemia (S-S) at sea level, in subjects with hemoglobin S-C disease at an altitude of 6,000 feet, and in subjects with sickle cell trait (S-A) only at higher altitudes. In general, sensitivity to deoxygenation effects is proportional to the amount of hemoglobin S within the erythrocyte. However, this rule need not apply uniformly to all tissues. In the present case there was sufficient autoinfarction of the spleen of long standing to indicate that intrasinusoidal sickling had occurred in that organ on many occasions in the past, albeit to small degree. Shrunken spleens with evidence of old infarction were found in the two patients with S-C disease dying of postpartum hemorrhage cited by Smith and Conley [*7*] as well as in the presumptive case described in detail by Vance and Fisher [*21*]. A possible explanation is that in this case there was an usually large proportion of hemoglobin S (62 per cent) for S-C disease. It has been suggested that the degree of sickling and the severity of the disease is directly proportionate to the percentage of hemoglobin S present in the individual case [*31*].

The mechanism of intravascular sickling in the lungs, brain and kidneys may be either the same as that which produced the initial insult to the bone marrow, or it may be secondary to lowered intracapillary oxygen tension within these organs, secondary to the fat emboli. Certainly in the lung the lodgement of lipid globules at the capillary level would serve to develop a capillary-alveolar block, depressing further and more acutely the capillary oxygen tension and promoting further sickling. It is likewise easy to visualize the interference with glomerular circulation attendant upon embolization of lipid globules followed by intracapillary sickling, and a similar cycle is equally plausible in terminal cerebral vessels. It is notable that embolic fat was found only in organs with capillary circulation; the liver and adrenal which have sinusoidal circulations showed no embolic fat, merely a greater or lesser degree of intrasinusoidal sickling. In addition to the mechanical effects of embolic fat on local circulation, the presence of marrow fat in the circulating blood can only serve to increase the viscosity of the blood, thereby accelerating the sickling phenomenon.

The patient did not survive long enough for the development of overt areas of cerebral necrosis and softening such as described by Wade and Stevenson [*20*] and Wertham, Mitchell and Angrist [*22*]; nor by the same token was coagulation necrosis seen in the bone marrow. It is a plausible inference that, had the patient survived, these changes would have occurred. The moderate hypertrophy of the left ventricle as well as the changes in the spleen indicate that systemic effects of S-C disease can be present for some time before overt symptoms appear.

The following pathogenetic sequence is postulated: An initial insult to the hyperplastic bone marrow produced acute hemorrhagic infarction with disruption of the marrow architecture. Intracellular fat and intact fat cells were displaced from the marrow into sinusoids and underwent embolic dispersion to the lung, brain and kidneys, producing local decreased capillary oxygen tension which led to intravascular sickling in these sites with the formation of conglutinative thromboses intermixed with some degree of fibrin thrombosis. Intrasinusoidal sickling occurred in the liver and adrenal glands secondary to systemic anoxia attendant upon the preceding changes.

The nature of the splenic lesions is of some interest. In pure homozygous hemoglobin C disease splenomegaly is uniformly present. Four spleens removed from patients with this disease [*2–5*] weighed from 720 to 2,300 gm. The sinusoids were engorged with erythrocytes and were markedly dilated. There was no evidence of infarction. The white pulp was normal. In sickle cell anemia (pure homozygous hemoglobin S disease) it is not uncommon to find splenomegaly in childhood, but progressive autoinfarction with the deposition of siderofibrotic nodules secondary to intrasinusoidal and intraarteriolar sickling and thrombosis is well recognized. In hemoglobin S-C disease the findings are variable. In Edington's five cases [*22*] the spleens weighed from 315 to 850 gm. In the three young women dying suddenly during pregnancy (635 gm., 850 gm., 427 gm.) there was no scarring, no siderofibrotic nodule formation, and deposition of iron pigment only in the endothelial cells lining sinusoids and in the capsule. In the two men dying with infection (315 gm., 548 gm.) only the smaller spleen was described as hard and fibrotic; however, siderofibrotic nodules were found in both. In the present case as well as in the case reported by Vance and Fisher [*21*] and in the two cases cited by Smith and Conley [*7*] the spleens were all small and shrunken, none weighing more than 75 gm. Smith and Conley [*7*] provide no micro-

scopic description of the spleen. The spleen in the present case and in the case of Vance and Fisher [*21*] was morphologically indistinguishable from those seen in cases of sickle cell anemia of long standing. The spleen is the principal organ to show long-standing effects of S-C disease, a product both of the unusually large proportion of hemoglobin S and the fact that the spleen has a complex sinusoidal bed in which stasis and low oxygen tension are maximal.

SUMMARY

1. A case of hemoglobin S-C disease in a twenty-eight year old Negro man dying in crisis is presented.

2. Postmortem examination revealed extensive intravascular sickling with the formation of conglutinative thrombi in the lungs, liver, kidneys, adrenals and brain. Acute infarction of the bone marrow by sickled erythrocytes was present. Extensive dissemination of embolic fat and marrow elements was found in the lungs, and fat emboli were present in the brain and glomeruli. The spleen was shrunken, showing extensive autoinfarction and siderofibrotic nodules.

3. The variability of the clinical picture of S-C disease is dependent upon the proportion of hemoglobin S that is present. The severity of the crisis and the fatal outcome in this patient is explained by the unusually high concentration of hemoglobin S, namely 62 per cent.

4. Crisis in this disease is due to intravascular sickling. A possible pathogenetic sequence is suggested, emphasizing the release of fat from infarcted bone marrow, resulting in increased viscosity of the blood, systemic hypoxia as a result of the capillary-alveolar block produced by pulmonary fat embolism, and further intravascular sickling in the lung and other organs as a result of both local deoxygenation and systemic hypoxia. The nature of the initial insult to the bone marrow remains obscure.

Acknowledgment: We acknowledge with thanks the hemoglobin electrophoreses and calculations performed by Miss Lee Burnett, M.S.

ADDENDUM

Shortly after this article was accepted for publication, Shelley and Curtis [*32*] reported three cases of bone marrow and fat embolism in sickling states. One was the case previously described by Eastman [*25*] of hemoglobin S-C disease with crisis and death in late pregnancy. The other two cases are of sickle cell anemia [S-S] in adolescent male Negroes, both of whom had been so diagnosed some time before the terminal episode. The observations in these cases are essentially compatible with those in the case reported here.

Also, Lau [*33*] describes a patient who died with multiple pulmonary infarctions and extensive intravascular sickling as a result of hemoglobin S-C disease. The spleen weighed 10 gm. and had undergone "autoinfarction." Likewise, a 23 gm. spleen was found at autopsy in a fifty year old Negro man with hemoglobin S-C disease who died in crisis following trauma [*34*].

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Electrocardiographic and Radiographic Findings in Acute Arsenic Poisoning*

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ARSENIC is not a toxic element in its metallic form. Its compounds, however, both organic and inorganic, are extremely poisonous and have been used for homicidal purposes through the ages. Easy availability of the compounds of this metal and lack of distinct flavor of its most widely used compound, arsenic trioxide (As_2O_3), make this substance one of the favorite tools for mass poisoning or homicidal purposes. Accidental poisoning with its compounds would also be expected to be relatively high due to the wide use of arsenic trioxide as a rat poison. A review of the literature, however, reveals a few reported cases of arsenic poisoning, and Lowbeer [*1*] states " . . . this case of fatal poisoning with arsenic is presented as a clinicopathologic conference in order to draw attention to the characteristic features of an entity that probably occurs more frequently than it is recognized." It is of interest that whenever a case of arsenic poisoning has been presented as a clinicopathologic diagnostic problem, the correct diagnosis usually has not been made [*1,2*].

CASE REPORT

A thirty-two year old Negro man was seen in the emergency room complaining of vague abdominal pain of three weeks' duration. In the three days prior to admission the pain had become more severe, and

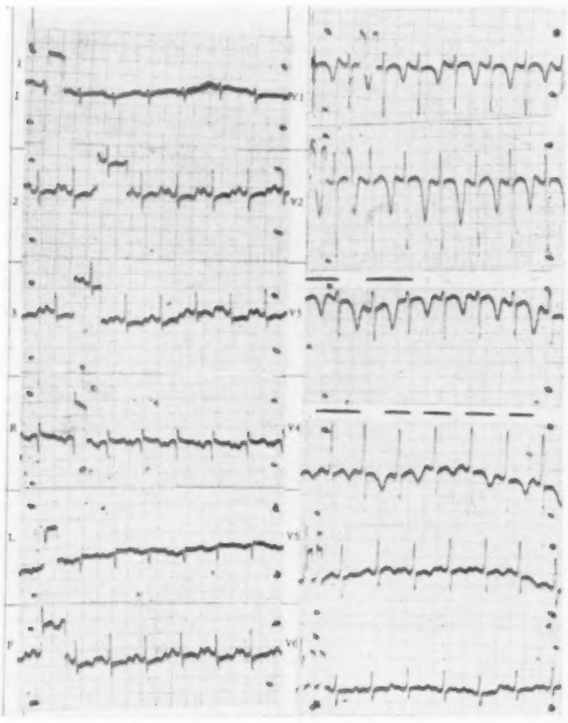


FIG. 1. Electrocardiogram showing deeply inverted T waves in V_1–V_5.



FIG. 2. Plain film of abdomen showing radiopaque material in the area of the stomach.

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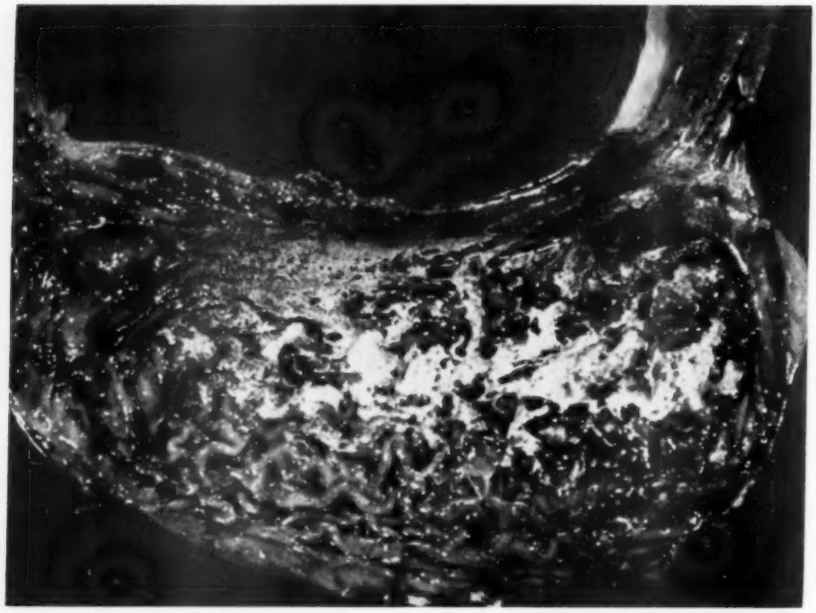


FIG. 3. Distal esophagus and stomach. The esophageal mucosa is shaggy and injected. Large quantities of white granular material (arsenic trioxide) are adherent to the gastric mucosa.

on the day of admission sharp, crampy epigastric pain had developed radiating to the lower part of the abdomen; he had vomited blood-tinged, brown material. There was no history of peptic ulcer, and both he and his wife denied having eaten canned or "left over" food or exposure to poisons.

On examination the patient was well developed and well nourished. He thrashed about in bed complaining of severe abdominal pain. The blood pressure was 70/30 mm. Hg.; respirations, 24; pulse, 100; and temperature, 37°C. The skin turgor was poor. The lungs were clear to percussion and auscultation. The heart was normal in size with a soft, apical, blowing murmur occupying one-half of systole with poor transmission to the axilla. The peripheral pulses were of poor quality and symmetrical. The abdomen was "board-like" and diffusely tender with hypoactive bowel sounds. No abdominal scars were present, and no organs or masses were palpable.



FIG. 4. Jejunum with intense mucosal congestion.

Hemogram revealed a hematocrit of 53 and a white cell count of 4,000 with 60 per cent granulocytes and 40 per cent lymphocytes. Urinalysis showed a trace of acetone and a trace of sugar. Serum amylase was 242 per cent of normal. Gastric aspiration yielded brown guaiac-negative liquid. The stool was also guaiac-negative. An electrocardiogram (Fig. 1) showed sinus tachycardia and changes indicative of extensive anterior myocardial ischemia. A roentgenogram of the chest showed no abnormalities. A plain film of the abdomen (Fig. 2) showed radiopaque material in the region of the stomach and pancreas.

The patient went into profound shock shortly after admission. He was given 2 units of blood, 1 unit of dextran, 3 L. of 5 per cent dextrose in water and 3 ampuls of levophed without blood pressure response. His condition deteriorated rapidly, and he died with a generalized convulsion three hours after arrival. The case was referred to the Coroner's Office for further study and investigation.

At autopsy, the patient was well developed and well nourished, weighing 160 pounds. A phlebotomy wound was present above the right medial malleolus. The pleural cavities each contained approximately



FIG. 5. Esophagus. Diffuse mucosal ulceration with bacterial colonies on surface. The submucosal vessels are markedly dilated. A cluster of arsenic trioxide crystals is present.

200 cc. of clear, straw-colored fluid, and 100 cc. of similar fluid was present in the pericardium. The heart was dilated with multiple focal and confluent areas of subepicardial hemorrhagic extravasation measuring from 2 to 5 mm. over the anterior aspect of the interventricular septum. The coronaries were widely patent. The lungs were congested and edematous. The esophageal mucosa was injected and shaggy. The stomach contained a few drops of brown mucoid fluid. Its mucous membrane was diffusely hemorrhagic with masses of granular white crystalline material adherent in several areas. (Fig. 3.) The small intestine contained brown seromucoid fluid. Its mucous membrane was dark mahogany brown, flecked with focal hemorrhagic zones. (Fig. 4.) The colon contained yellow-green, watery stool. The liver presented a mottled yellowish brown and reddish brown parenchyma with poor preservation of the usual hepatic architectural landmarks. The kidneys showed cortical swelling and marked congestion.

On microscopic examination the esophagus showed extensive ulceration and marked dilation of the submucosal vessels with bacterial colonies and small clusters of crystals adherent to the surface. (Fig. 5.) The myocardium appeared normal. The stomach revealed hemorrhagic mucosal necrosis with masses of similar crystalline material on its surface. (Fig. 6.) The small intestine showed superficial mucosal necrosis and marked mucosal congestion. The liver cords were fragmented. The renal tubular epithelial cells were swollen and degenerated. The brain revealed perivascular hemorrhages and necrosis. The viscera generally were markedly congested.

The crystals adherent to the surfaces of the stomach and esophagus were identical in structure with those obtained from a container of commercial rat poison

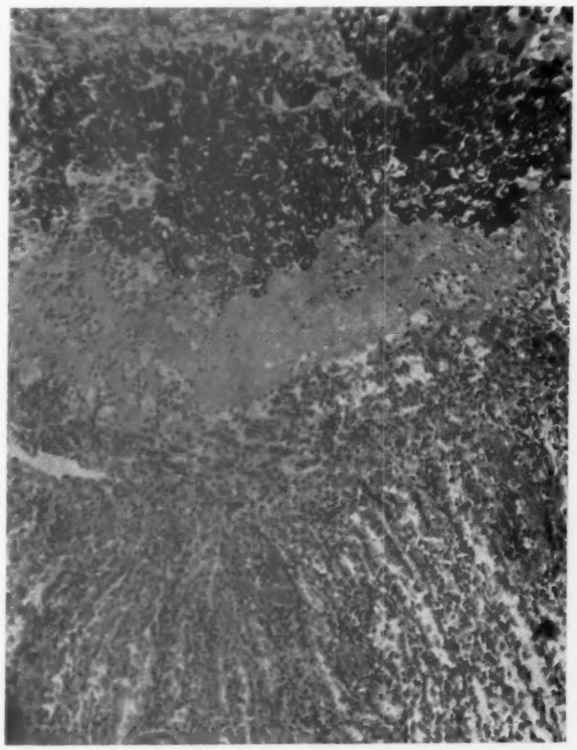


FIG. 6. Stomach. Large masses of arsenic trioxide crystals are adherent to the mucosa.

(Rose's Rat Killer), containing 99.08 per cent arsenic trioxide.

Chemical analyses of the viscera for the presence of arsenic yielded the following results (all figures in mg./100 gm.): brain, 0.3; liver, 8.1; kidneys, 3.0; spleen, 0.63; hair, 40.0; nails, 5.0; blood, 0.16; and small intestine, 3.5.

The police were notified immediately following establishment of the fact that death was due to arsenic poisoning. The wife was interrogated and admitted that during the past three weeks she had been spreading approximately a teaspoonful of rat poison on the sandwiches which the patient took to work each day. On the day he was admitted to the hospital, she had sprinkled about two tablespoonfuls on his sandwiches. She was arrested, indicted for murder in the first degree and tried before three judges. Her defense was that she had not intended to kill the patient but had merely wanted to make him sick. She was found guilty and sentenced to the penitentiary for life.

COMMENTS

Review of the literature of the last fifteen years reveals few references to arsenic poisoning. Gonzales [*3*] reported 145 suicidal deaths from inorganic arsenic compounds between 1918 and 1951 in New York City. During the same interval there were 114 fatal cases of accidental poisoning with arsenic compounds, mostly arsenic trioxide. Arsine, AsH_3, a colorless gas with a light garlic odor, is the next most commonly involved compound. Arsine is occasionally formed during the processing of ores and chemicals containing arsenic, and it may escape detection until it is present in sufficient concentration to cause serious or fatal poisoning.

The signs and symptoms of arsenic poisoning vary with the amount ingested, the rates of absorption and excretion, or, in the case of arsine, the time of exposure and the concentration of gas in the atmosphere [*3*].

Inorganic arsenic compounds are strong protoplasmic poisons producing changes in all organs but involving mainly the capillaries. Arsenic accumulates preferentially in the liver, causing acute liver necrosis. Its mode of action is believed to be its combination with enzymes containing sulfhydryl groups which results in their inactivation. The minimal fatal dose has been estimated at 0.1 to 0.2 gm.

Electrocardiographic changes in arsine poisoning have been described by Josephson et al. [*4,5*] who conclude that "the electrocardiographic changes produced in humans by arsine poisoning seem to offer the most sensitive means of diagnosis so far discovered." The so-called characteristic electrocardiographic changes observed by Josephson were tall asymmetrical, peaked T waves in all cases except one in which the T waves were inverted.

The electrocardiographic findings in this case are not similar to those reported by Josephson [*4*]. In view of the anatomic changes caused by arsenic we would doubt that typical electrocardiographic changes due to arsenic poisoning actually do occur. It is probable that the electrocardiographic changes depend upon the degree of damage to the coronary vasculature and the myocardium. Since arsenic interferes with the function of respiratory enzymes, it is likely that the electrocardiographic changes will be comparable to those produced by ischemia of the myocardium from any cause. The ultimate electrocardiographic abnormalities reflect the distribution and degree of the myocardial disturbance. Thus, in our case, the electrocardiogram showed "transmural ischemia." If the involvement were less marked and perhaps limited to the subendocardial musculature, the T waves would probably be tall and peaked as in the cases reported by Josephson [*4*].

The correct diagnosis in our case, as in most other reported cases, was not considered prior to death. Lowbeer [*1*], discussing a similar case, states "several astute internists were consulted, but none of them suspected arsenic or any other poison, nor was such a diagnosis suggested by the attending physicians." The clinician, whether internist or surgeon, must constantly bear in mind the axiom that there is hardly a sign or symptom of natural disease that cannot be mimicked by poison. In any obscure diagnostic problem, consideration must always be given to the etiologic possibility of exposure to exogenous toxic substances. The presence of radiopaque material in the stomach enhances this possibility.

SUMMARY

A case of fatal arsenic poisoning is reported. The electrocardiographic and radiographic findings are presented, and an explanation is offered for the changes noted in tracings.

Arsenic or other heavy metal poisoning should be given diagnostic consideration in any acute abdominal syndrome whose causation is not readily apparent. The presence of radiopaque material in the stomach in such instances furnishes strong evidence of metallic ingestion as the basis of the clinical picture.

Acknowledgment: The photographs for Figures 1 and 2 were made by the Photography Department of the Cuyahoga County Hospital. The remaining photographs and photomicrographs were prepared by Mr. Sid Pancner, Staff Photographer at the Cuyahoga County Coroner's Office. The chemical analyses were carried out by Irving Sunshine, Ph.D., Toxicologist at the Cuyahoga County Coroner's Office.

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Renal Tubular Acidosis and Potassium Loss*

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MORE than two decades have elapsed since Lightwood [*1*], Butler [*2*] and Albright [*3*] reported the first cases of a syndrome that in recent years has been characterized under the name of renal tubular acidosis. The cases appearing in adults now total about thirty-six; the number reported in the pediatric literature is considerably more. In 1951 Pines and Mudge [*4*] found fourteen previously reported cases and added three of their own. Foss, Schreiner, Milne, Wilensky, Eastham, Brooks, and Reynolds [*5–12*] have added one or more cases since then. Certain "underlying diseases" have been associated with this syndrome, including chronic pyelonephritis, sarcoidosis, sulfonamide toxicity and uterosigmoid transplants [*13*]. A case report has recently appeared in which the patient's urine contained Bence Jones protein [*14*].

Patients with renal tubular acidosis are usually women, with a history which may include polydipsia, polyuria, attacks of weakness, renal colic, and episodes compatible with the diagnosis of pyelonephritis. They are frequently asthenic, apathetic, easily fatigued and may suffer from osteomalacia. The alteration in homeostasis that helps to produce these symptoms depends to a large extent on a loss of cation that results from the inability of the kidney to produce an acid urine. A systemic acidosis develops, characterized by hyperchloremia, hypocapnea, hyponatremia, and lowered plasma pH, with an alkaline or weakly acid urine. Some patients also have low serum potassium concentrations and some suffer from hypocalcemia and hypophosphatemia. There are also a number whose base-losing diathesis involves both calcium and potassium ions. This syndrome can be distinguished from the de Toni-Fanconi syndrome by the absence of glycosuria and aminoaciduria.

Because of the infrequency with which the syndrome occurs and the presence of several unusual features in the patient to be described, it was thought worthwhile to make this patient the subject of a case report and a metabolic study.

CASE REPORT

M. F. (Chart No. 48590-57) is a thirty-six year old Negro woman, a Panama-born domestic and mother of two, who was admitted to the First Medical Division of Bellevue Hospital in September 1957 with a two-day history of nausea and vomiting, and a thirty-six-hour history of weakness of all extremities, progressive to diffuse flaccid paralysis. She gave a history of polydipsia and polyuria with nocturia for approximately ten years. Two years prior to admission she had an episode of severe left-sided intermittent colicky abdominal pain associated with fever, chills and dysuria. She received some medication from her family physician, the nature of which is unknown but may have been a sulfonamide, and the symptoms subsided during the next five days. She denies hematuria at that time, but was told she had albuminuria. Following this episode the severity of her polyuria and polydipsia markedly increased, and she noted a decrease in appetite with a gradual weight loss of 30 pounds during the next twenty-four months.

In December 1955 the patient was admitted to the Gorgas Hospital in the Panama Canal Zone complaining of progressive muscular weakness and myalgias. She was unable to walk or raise her head and appeared markedly apathetic and withdrawn. Her heart rate was 76 per minute; blood pressure, 124/72 mm. Hg; temperature, 98.6°F. orally. The physical examination was essentially within normal limits. Laboratory studies on admission revealed: white blood count, 17,250 per cu. mm.; hemoglobin, 14 gm. per cent; erythrocyte sedimentation rate, 45 mm. in the first hour; the urine contained 1-plus albumin and "some pus cells." She remained lethargic for two days but then gradually regained her strength. She received a short course of penicillin and streptomycin and was discharged with the diagnosis of "conversion reaction and neutrophilia, cause unknown."

During the ensuing ten months she had three or four similar self-limited episodes, all preceded by

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excessive beer drinking, and followed by an increase in the degree of polyuria and polydipsia. About five days prior to admission to Bellevue Hospital she flew from Panama to the United States. Two days prior to admission she noted an increase in the degree of polyuria and polydipsia and had several episodes of nausea and vomiting. Thirty-six hours prior to admission she noted the onset of progressive weakness of her extremities, without any sensory loss, and without difficulty in breathing or talking. Because of these symptoms she presented herself at Bellevue Hospital.

The family history revealed her mother and sister to have hypertension. There is no knowledge of any familial renal or neurological disease. No relative had similar symptomatology. Review of systems revealed that the patient had had severe constipation for ten years. She had undergone left oophorectomy for "tumor" in 1944. She denied knowledge of previous ingestion of sulfonamides, excessive use of cathartics, vitamin D or milk. She denied any knowledge of hypertension, edema, hematuria or nephritis.

On admission the patient appeared as a thin, poorly developed, sleepy Negro woman in no acute distress but unable to stand. She was not dyspneic, orthopneic or edematous. The blood pressure was 130/80 mm. Hg; heart rate, 60 per minute; and temperature, 99.6°F. rectally. The skin was dry. A non-tender left inguinal node measuring 2 cm. and a left axillary node measuring 1 cm. were noted. Examination of the eyes, ears, nose and throat revealed no abnormalities. The chest was clear to auscultation and percussion. A grade 1 systolic murmur over the precordium was heard. The abdomen was doughy and soft, the liver and spleen not felt. The kidneys were palpable bilaterally but were non-tender and not thought to be enlarged. There was a small urethral caruncle. Neurological examination revealed diffuse and marked weakness of the muscles of all extremities, without evidence of wasting. There were no tremors or fasciculations and the deep tendon reflexes were intact. No Chvostek sign or abnormal reflex was present. The sensory examination was normal.

Laboratory studies revealed the following: hemoglobin, 14 gm. per cent; hematocrit, 35 per cent; white blood count, 15,950 per cu. mm. with a normal differential, the leukocytosis disappearing later in the course; the erythrocyte sedimentation rate (Westergren) varied between 80 and 100 mm. in the first hour. Urinalysis revealed a specific gravity of 1.002; on a concentration test after sixteen hours of hydropenia the specific gravity never exceeded 1.008. A trace to 1-plus of protein was persistently present in the urine and the urinary sediment contained an occasional white blood cell. The urine was persistently alkaline to nitrazine paper and had a pH of 6.75, by glass electrode. There were never any reducing substances present in the urine and the total urinary alpha-aminoacid nitrogen was normal. The Sulkowitch test for urinary calcium was 3-plus, with a



FIG. 1. Intravenous pyelogram illustrating the presence of calcifications within the renal parenchyma.

control of 1-plus. The phenolsulfonphthalein excretion was 55 per cent in two hours. Urine culture for pyogens was negative. The blood urea nitrogen ranged from 5 to 10 mg. per 100 cc. The arterial blood pH was 7.29. Electrolyte studies revealed the serum sodium to range from 132 to 140 mEq./L.; serum potassium ranged from 1.5 to 2.1 mEq./L.; serum chloride from 110 to 112 mEq./L.; and carbon dioxide content was 14.8 mEq./L. The serum calcium was 11 mg. per 100 cc. and the serum phosphorus ranged from 2.5 to 4.0 mg. per 100 cc. The serum albumin was 4.3 to 5.0 gm. per 100 cc.; and the globulin, 3.5 to 3.9 gm. per 100 cc. The cephalin-cholesterol flocculation test was 3-plus and the alkaline phosphatase was 3.0 Bodansky units per 100 cc. The fasting and two-hour postprandial blood sugars were normal. Results of the Mazzini test were negative, as were lupus erythematosus cell preparations. Roentgen examinations of the chest and survey of the skeletal system were normal. The lamina dura was intact. There were small bilateral calcific densities within the renal shadows. (Fig. 1.) The intravenous pyelogram was normal. The purified protein derivative No. 1 (tuberculin) test was negative and No. 2 positive. Electrophoretic studies of the serum revealed moderately diffuse and marked elevation of the gamma globulin; alpha-1, alpha-2 and beta globulin were normal and there was moderate reduction in albumin. Ultracentrifugation of the serum did not show any component with a sedimentation coefficient greater than 7S. The proteinuria consisted of albumin and globulins, which were non-specific. An abnormal histone was also found.

Examination of the cerebrospinal fluid revealed normal pressure, a protein content of 44 mg. per 100 cc. and no cells. The colloidal gold curve was abnormal, 4443210000.

Renal biopsy revealed a mild fibrosis surrounding some of the Bowman's capsules, areas of thickening of glomerular basement membranes, and hyaline and protein casts in several tubules. One glomerulus was completely hyalinized. The arteries and arterioles were normal. The interstitial tissue showed minimal

fibrosis and lymphocytic infiltration. Focal tubular atrophy was present but no evidence of hydropic degeneration of the tubular lining cells was found. No specific diagnosis could be made by the pathologist. Biopsies of the gastrocnemius and deltoid muscles were unrevealing.

Electrocardiograms were compatible with hypokalemia (see Comments). The following characteristics made the diagnosis compatible with that of renal tubular acidosis: (1) the presence of systemic acidosis as manifested by hyperchloremia, hypocapnia, and low arterial pH; (2) the presence of defective urinary acidification as manifested by alkaline or weakly acid urine, excessive excretion of sodium, potassium and calcium; (3) the further evidence of tubular dysfunction as manifested by polyuria, polydipsia, hyposthenuria and dehydration; and (4) the presence of renal calcification and probable history of renal infection.

Following a metabolic study the patient was discharged on a daily regimen of 80 mEq. of potassium (as potassium citrate) and 82 mEq. of sodium bicarbonate. She gradually gained weight and felt better than she had at any time during the previous two years. There was a decided lessening in the degree of polyuria and polydipsia. The serum electrolyte values one month after discharge were as follows: sodium, 127 mEq./L.; potassium, 4.1 mEq./L.; chloride, 101 mEq./L.; carbon dioxide combining power, 20 mEq./L. About five weeks after the patient's discharge there suddenly developed pitting edema of the arms and legs and facial edema. There was a further decrease in urinary output and her weight rose to 20 pounds greater than on discharge. Three days prior to the onset of this event, electrolyte values had been determined as follows: serum sodium, 160 mEq./L.; serum potassium, 4.2 mEq./L.; serum chloride, 135 mEq./L.; carbon dioxide combining power, 24.4 mEq./L.; serum calcium, 15.8 mg./100 cc. The patient stopped taking her medicine and, with a sudden increase in polyuria, noted a disappearance of the edema. We have no explanation of this electrolyte picture.

The patient was seen again two weeks after this episode, during which time she had not taken any replacement therapy. Her electrolytes at this time were as follows: serum sodium, 140 mEq./L.; serum potassium, 3.2 mEq./L.; serum chloride, 119 mEq./L.; carbon dioxide combining power, 16.8 mEq./L.; serum calcium, 11.8 mg./100 cc. There was no change in the serum total protein. The erythrocyte sedimentation rate was 90 mm. in the first hour. The urine specific gravity was 1.006. A trace of protein and an occasional white blood cell was present. The urine Sulkowitch test was 3-plus. On physical examination the blood pressure was 110/70 mm. Hg; the heart rate was 80 per minute; respirations were 20 per minute. The entire examination was within normal limits except for tenderness in the right upper quadrant of the abdomen on deep palpation and 1-plus ankle edema on the left side.

A metabolic study was carried out to further elucidate the nature of the disease process. The patient was maintained throughout the study on a diet with fixed electrolyte components as follows: sodium, 15 mEq./day; potassium, 33 mEq./day; calcium, 108 mg./day; phosphorus, 450 mg./day. The study was divided into thirteen three-day periods. All blood specimens were obtained while fasting, prior to breakfast. The urine was collected in twenty-four-hour periods and aliquots were removed for study. The stool examinations were made on period pooled specimens.

During the control period the patient was asymptomatic despite severe potassium restriction and a negative potassium balance. She lost potassium in excess of 29 mEq. in the urine each day. The serum potassium concentration dropped to as low as 1.4 mEq./L. at one point. At the same time, on a restricted sodium intake, the sodium balance also was negative, while the calcium balance was borderline.

During replacement therapy the potassium balance became positive although the urinary loss continued to exceed 15 mEq./day. The serum value rose to low normal levels. This direct relationship between increase in potassium intake and a rise in the serum concentration, along with the persistent evidence of excessive urinary loss of potassium, points to the renal origin of the loss.

The patient's ability to tolerate such a low potassium intake asymptomatically may be associated with the low sodium intake employed in the present study [*15*]. Cannon et al. and others have noted an exaggeration of hypokalemic symptoms when excessive sodium is given in the diet, while on a low sodium diet these symptoms, and the tissue lesions as well, are less prominent [*16,17*]. Perhaps this fact may explain the absence, in the present case, of any changes pathognomonic of hypokalemia in either renal or muscle biopsies.

It has also been noted that when serum potassium loss is gradual it is accompanied by an almost simultaneous decrease in the concentration of potassium on both sides of the muscle cell membrane, the intra- to extracellular potassium ratio remaining essentially unchanged. This may explain why muscle function can be preserved in gradually occurring severe hypokalemic states

TABLE I

BALANCE STUDIES

Test Period	Na (mEq./Day)			K (mEq./Day)				Ca (mEq./Day)				Phosphorus (mg./Day)		
	Intake	Urinary Output	Balance	Intake	Urinary Output	Output Feces	Balance	Intake	Urinary Output	Output Feces	Balance	Intake	Urinary Output	Balance
Control:														
No. 1	15	14	−	33	45	↑	−14	108	34	↑	+21	450	413	−
No. 2	15	23	−8	33	42	6	−11	108	53	159	+2	450	340	−
No. 3	15	29	−14	33	38	↓	−7	108	58	↓	−3	450	308	−
Diamox:														
No. 1	15	35	−20	33	33	↑	−3	108	47	↑	−239	450	270	−
No. 2	15	42	−27	33	29	6	+1	108	57	600	−249	450	229	−
Control:						↓				↓				
No. 4	15	26	−9	33	37	..	−4	108	37	....	−	450	229	−
Diamox:														
No. 3	15	27	−12	33	21	..	+12	108	43	....	−	450	170	±
No. 4	15	33	−18	33	19	..	+14	108	63	....	−	450	191	±
Rx:														
No. 1	15	32	−17	91	24	↑	+59	108	15	↑	−267	450	200	±
No. 2	15	31	−16	62	19	24	+35	108	18	1080	−270	450	215	±
No. 3	66	47	+19	91	21	↓	+62	108	21	↓	−273	450	173	±
No. 4	87	74	+13	91	19	↑	+65	108	15	↑	−207	450	72	+
No. 5	95	107	−12	106	27	14	+72	108	15	600	−207	450	52	+
						↓				↓				

[*18,19*]. In familial periodic paralysis there is marked alteration of this ratio, which may account for the occurrence of muscle weakness with serum potassium levels as high as 3 mEq./L.

Our patient weighed 42 kg. The normal total body potassium in a woman of this weight is about 1,500 mEq. The body deficit of potassium with a serum concentration of 2 mEq./L. in the presence of systemic acidosis is presumably in excess of 10 per cent, or greater than 150 mEq. [*20*]. The degree of positive potassium balance that developed during the replacement period is also in keeping with this figure. During the period of potassium replacement without added bicarbonate, the loss of urinary sodium was temporarily increased. This may possibly be due to the diuretic effect of potassium salts. During sodium replacement the sodium balance became positive, indicating that there was depletion of body sodium as well as of potassium. The decrease in urinary calcium excretion during the replacement period was probably secondary to the decrease in obligatory base loss that occurred with correction of the acidosis.

During an acetazoleamide (Diamox®) test period there was a fall in serum sodium concentration, an increase in renal sodium loss and a fall in serum bicarbonate concentration. The latter reached a level of 9 mEq./L. This confirms the earlier work of Kaye [*21*], showing that the carbonic anhydrase mechanism is intact in renal tubular acidosis.

During the acetazoleamide test period there was essentially no potassium diuresis or change in serum potassium. This is difficult to explain since previous work [*21*] showed an increase in renal potassium loss under similar circumstances except for more nearly normal serum potassium levels. This variation may be related to the altered response. In addition, the large outpouring of sodium which took place in this case may have had a potassium-sparing effect at the tubular level. (Tables I and II.)

At her lowest serum potassium levels, in the range of 1.4 mEq./L., the patient's electrocardiogram showed the following characteristics: (1) low T waves in the standard and augmented unipolar leads, the highest T measuring 1.3 mm. The maximum QRS amplitude in these leads was 11 mm. in lead S2. (2) ST segments flat and measuring 0.11 seconds in duration. (3) QT interval 0.40 seconds in duration. (4) T waves in precordial leads measuring as high as 5.5 mm. at full standardization (V3), followed by prominent U waves 2 mm. in height. (Fig. 2.)

While on potassium citrate therapy, with serum potassium levels approximating 3.2 mEq./L., the tracing showed changes as follows: (1) T waves in standard and precordial leads slightly increased in prominence, the highest 1.5 mm. The maximum QRS amplitude in these leads was 9.5 mm. in lead S2. (2) ST segments flat and measuring 0.15 seconds in

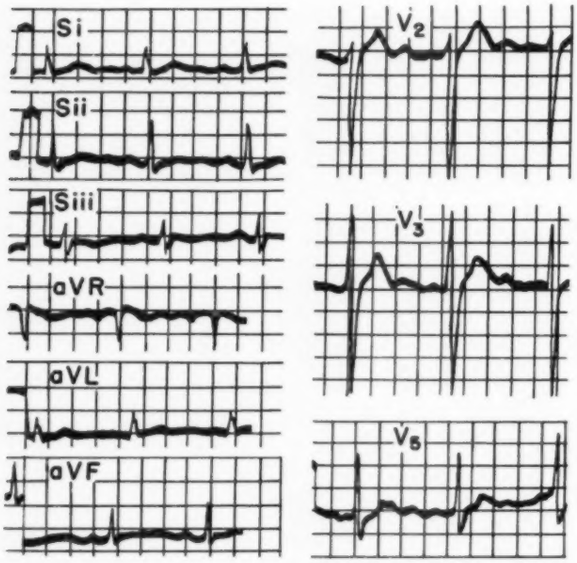


FIG. 2. Electrocardiogram taken with serum potassium in the range of 1.4 mEq./L.

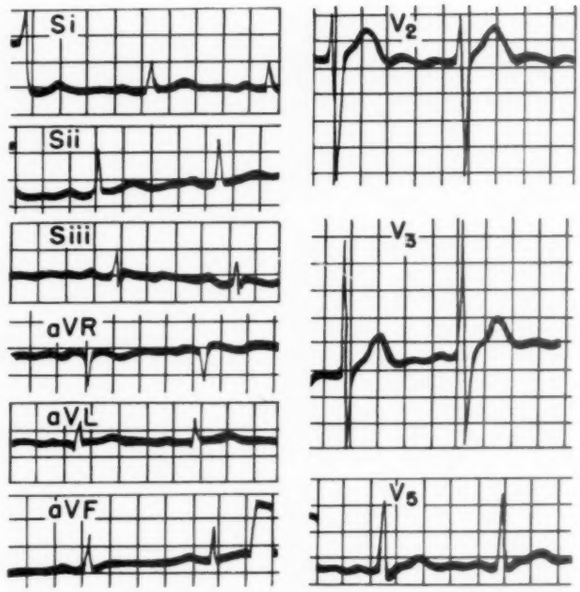


FIG. 3. Electrocardiogram taken with patient under potassium citrate therapy; serum potassium in the range of 3.2 mEq./L.

duration. (3) QT interval of 0.36 seconds in duration. (4) precordial T waves of slightly increased prominence, measuring 6.0 mm. at full standardization (V3), followed by slightly less prominent U waves, maximally 1.5 mm. in height. (Fig. 3.)

The relative paucity of marked hypokalemic electrocardiographic findings is of note, considering the low serum potassium levels obtained. Bellet [*22*] classifies electrocardiographic signs of hypokalemia into several patterns. The tracings in this case most clearly fit his pattern in which the T wave is followed by a U wave of almost equal amplitude, with the downstroke of the T almost reaching the isoelectric line.

The electrocardiogram taken when the patient's serum potassium was in the range of 3.2 mEq./L. showed a remarkably small increment of change. The increased T wave prominence,

TABLE II
SERUM LEVELS

Test Period	Sodium (mEq./L.)	Potassium (mEq./L.)	Chloride (mEq./L.)	Bicarbonate (mEq./L.)	Calcium (mg. %)	Inorganic Phosphorus (mg. %)	pH Venous Blood
Control:							
Nos. 1, 2, 3	138	2.0	110.5	14.5	11.1	3.4	7.31
Diamox:							
Nos. 1, 2	126	2.1	113	10.7	....	...	7.23
Control:							
No. 4	127	1.4	106	14.2	11.2	3.6	7.33
Diamox:							
Nos. 3, 4	118	1.9	102	9.1	10.3	4.0	7.23
Rx, Nos. 1, 2:							
K citrate	130	3.3	114	17.3	10.3	...	7.22
Rx, No. 3:							
K citrate, $NaHCO_3$	131	3.2	114	21.5	11.3	2.3	7.37
Rx, Nos. 4, 5:							
K citrate, $NaHCO_3$	136	3.5	105	22.3	10.6	3.2	7.34

shortening of the ST segments and QT intervals, and decreased amplitude of the U waves, are all changes toward normal, slight in degree.

In this case, clearly, the low serum potassium levels did not cause the marked electrocardiographic changes which might have been expected. A possible explanation is that, as far as the electrical phenomena within the myocardium are concerned, the intra- to extracellular potassium ratio is the key; or, as Schwartz et al. suggest [*23*], the intramyocardial potassium concentrations may be the important factor, regardless of the serum potassium levels. A delay in the electrocardiographic response to change in serum potassium level and potassium balance has previously been noted by Schwartz et al. [*23*], further suggesting that it is not the serum potassium level itself which is significant.

It is interesting that, while the patient's skeletal muscles changed from a markedly paretic to a normally functioning state, the electrocardiogram and the serum potassium levels showed essentially no change. There is clearly a functional difference between myocardium and skeletal muscle in their relation to potassium levels, probably again based more on intracellular levels or intra:extracellular ratios than on serum potassium levels [*24*].

COMMENTS

As already noted, a number of different diseases have been associated with renal tubular acidosis. In addition, there are a number of reported cases in which there was a congenital, or at least familial association. It is difficult to establish clearly whether we are dealing with a single disease entity or a group of diseases which have so altered renal function as to produce the clinical picture of renal tubular acidosis. Chronic pyelonephritis is the disease most often associated with renal tubular acidosis; however, the very nature of the tubular defect results in renal calcification and obstruction, which predispose to secondary infection. Certainly in the overwhelming number of patients with chronic pyelonephritis renal tubular acidosis as a complication never develops.

No definite conclusion about the underlying process in the patient reported in this study has been made. Her history is compatible with that of pyelonephritis, although the urine culture taken during her admission was sterile, and the kidney biopsy was equivocal. The polyuria preceded any overt symptoms of renal infection. It also antedated the occasion upon which she may have received sulfonamide therapy. Because of the patient's elevated erythrocyte sedimentation rate, elevated globulin, and a recent report linking sarcoid and renal tubular acidosis [*8*], she was further investigated with this disease in mind. The Kveim test biopsy and metacarpal x-ray films revealed no abnormalities. A histone was detected as part of the proteinuria. Lawlor and Osserman [*26*] have noted the presence of histones in the urine of three of seven proved cases of sarcoid, but the full significance of this finding has not as yet been determined.

As regards family history, no other family member reported symptoms suggestive of renal tubular acidosis. The electrolyte pattern of this patient's brother was normal.

Defect in Renal Tubular Acidosis. With further understanding of the mechanisms involved in the maintenance of body fluid pH, a clearer view of the defect present in renal tubular acidosis has appeared. The following mechanisms have been proposed:

1. Failure of ammonia excretion [*31,32*] was implicated because it was noted, in cases of this disease, that even after acid loading with ammonium chloride the urinary ammonia level was low. However, Latner and Burnard [*33*] were able to show that this phenomenon was secondary to the presence of an alkaline urine in the distal tubule, under which circumstances the ammonia-secreting mechanism is physiologically inhibited. By the infusion of sodium dihydrogen phosphate a normal acidity was obtained and subsequently the amount of ammonia produced was normal.

2. The inhibition of cellular carbonic anhydrase was noted, in normal subjects, to produce an electrolyte pattern similar to that seen in renal tubular acidosis. However, Kaye [*21*] showed, in a case of this disease, a normal response to the administration of carbonic anhydrase inhibitor when the plasma bicarbonate was raised to a normal level. We were able to show a significant response even in the presence of a depressed plasma bicarbonate concentration.

3. Latner and Burnard [*33*] found a high level of urinary bicarbonate excretion in patients with renal tubular acidosis in the resting state. They postulated that defective bicarbonate reabsorption in the proximal tubule was re-

sponsible for the development of the subsequent electrolyte disturbance. This would incriminate a specific phase of the sodium-hydrogen ion exchange mechanism.

4. Reynolds [*9*] has studied this same problem in detail in six patients. He found that when the serum bicarbonate concentration was raised to normal levels the tubular reabsorption of bicarbonate was normal. He also found that infused neutral phosphate was converted to the monosodium salt in a normal fashion. He concluded that the defect in renal tubular acidosis lay in inability of the tubule to secrete hydrogen ions against the increasing hydrogen ion gradient, such as normally occurs.

The conclusions of Latner and Burnard and of Reynolds are in disagreement in regard to the role of bicarbonate reabsorption in the development of electrolyte abnormalities in this disease. Also obscure is the mechanism for the development of the marked hyperchloremia in this disease. Whatever the basic defect, inability to acidify the urine is the initial event in a series of occurrences that alters homeostasis and leads to permanent damage to the kidneys and other organs.

When the normal base-saving mechanisms are compromised there is an obligatory loss of sodium, potassium and calcium ions in order to maintain electrical neutrality, while the loss of this fixed base leads to a systemic acidosis. The excessive loss of potassium ions can further compromise renal function because, while the capacity of the tubule cells to synthesize and excrete ammonia is normal in hypokalemic states, there is impairment of the ability to secrete a maximally acidified urine. In addition, the concentrating power of the tubule is impaired [*34*].

One can see how the basic difficulty in renal tubular acidosis is compounded by the electrolyte imbalance that it has produced. Hypokalemia can alter normal metabolic processes and is known to be associated with such symptoms as anorexia, nausea, mental depression and lethargy. Smooth and striated muscle (both skeletal and cardiac) function can be altered to produce intestinal ileus, respiratory paralysis and cardiac arrhythmias. The patient reported here complained of many of these non-specific symptoms. Her electrocardiographic abnormalities have already been noted. She had no arrhythmia.

Alteration in calcium homeostasis is a further defect that results from the inability to acidify the urine. Albright [*35*] and others have studied the problem of excessive calcium loss in renal tubular acidosis. The degree of calcium loss varies from patient to patient. The severity of this defect, and the amount of calcium that the person absorbs from the diet, will determine the symptoms and the degree of organic disease that develops. The excessive loss of calcium into the urine and a subsequent negative balance leads to osteomalacia. This entity may be suggested by a low calcium-phosphorus product and can produce pain in the bone, pseudofractures and deformities. Owing to a decrease in calcium solubility in alkaline urine, the tendency for calcium salts to precipitate is enhanced in renal tubular acidosis. The subsequent formation of calcium stones and/or nephrocalcinosis sets the stage for recurrent episodes of pyelonephritis. While the patient reported here had only one episode suggestive of renal colic, others have noted frequent passage of stones per urethra, hematuria, and constant pain in the flank [*4*].

With water and potassium balance already in a precarious state, excessive vomiting, diarrhea, frequent enemas, high fever or other situations demanding fluid and electrolyte homeostasis may precipitate any of the symptom-complexes already mentioned. The development of hypokalemic weakness in our patient was probably secondary to acute loss of potassium in the urine, related to excessive ingestion of beer.

Polyuria and polydipsia in this case presumably were secondary to inability to concentrate the urine, due to the obligatory loss of water accompanying fixed base in the urine and also to the development of tubule cell unresponsiveness to antidiuretic hormone [*10*].

Therapy. Therapy follows logically from an understanding of the altered physiologic mechanisms. Supplying extra base permits excretion of the acid metabolites without undue strain on the body stores. This is accomplished by giving varying amounts of sodium bicarbonate and sodium and potassium citrate. There is some disagreement as to the need of added vitamin D and calcium salts in the treatment of patients with changes of rickets. Albright and Pines and Mudge [*3,4,35*] advocate this, while Foss [*10*] has treated such patients without this addition to the regimen.

In our patient there was no evidence clinically upon which to make the diagnosis of osteomalacia. In addition the serum concentrations of calcium and phosphorus were within normal limits. Therapy was limited to administration of sodium bicarbonate and potassium citrate, given to a total of 162 mEq. of base each day.

SUMMARY

A case of renal tubular acidosis is presented. Etiological, historical, clinical and biochemical data associated with this syndrome are described. A metabolic study in the patient presented established the presence of a potassium-losing diathesis, and probably of a less severe sodium-losing diathesis. The renal carbonic anhydrase system appeared to be intact.

Features of note in the patient included an elevated erythrocyte sedimentation rate and serum globulin concentration and the presence of an abnormal histone in the urinary protein. A renal biopsy was performed, with equivocal findings. The significance of these points is discussed.

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Malabsorption Syndrome Associated with Metastatic Carcinoid Tumor*

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In recent years an increasing number of reports have appeared concerning the malignant carcinoid syndrome, which is characterized by diarrhea, flushing, ascites, heart murmurs and cachexia [*1–3*]. The diarrhea has been described as profuse and watery; we have found no data relevant to fat absorption and no mention of clinical or laboratory evidences of malabsorption which might accompany steatorrhea. Several authors have commented on the occurrence of pedal edema in the syndrome [*3–5*], but no satisfactory explanation for this finding, with the exception of cardiac decompensation found in one patient, has been offered.

During the past year we have observed a patient with malignant carcinoid, who has had all of the major signs and symptoms of the so-called "malabsorption syndrome." The pertinent findings are presented in this report.

CASE REPORT

L. A. (NYH No. 765747), a fifty-four year old white, married woman, was admitted to The New York Hospital for the first time on April 26, 1957, because of weight loss, abdominal pain and diarrhea.

The patient was in an excellent state of health until 1953, four years prior to her admission, when epigastric pain, nausea and intermittent vomiting developed. Over a period of several months her weight diminished from 205 to 145 pounds, and she was admitted to another hospital where cholecystectomy was performed. Following this procedure she felt well for about three months, and then noted recurrence of her symptoms with further weight loss of about 20 pounds. She re-entered the hospital and, following the repair of a hiatus hernia, improved symptomatically and gained 10 pounds. In 1955, two years before admission to The New York Hospital, she again noted abdominal pain, anorexia and weight loss. This episode led to reinvestigation and repair of a recurrent hiatus hernia, but with only partial relief of her distress. In 1956, one year prior to entering The New York Hospital, her pain returned, with radiation into the back. In November 1956, six months prior to admission, she began to have intermittent diarrhea and in January 1957, she first noted flushing of the face and upper thorax. Except for an attack of rheumatic fever at ten years of age, her past history was non-contributory.

On admission, physical examination revealed a cachectic, chronically ill-appearing, elderly woman with pulse 100, respirations 18, temperature 38.1°c., and blood pressure 110/70 mm. Hg. The left border of the heart was 1 cm. beyond the mid-clavicular line in the fifth intercostal space. The second pulmonic sound was louder than the second aortic sound and was accentuated. At the apex, the first mitral sound was louder than the second and there was a harsh, moderately loud systolic murmur which was transmitted to the axilla. In addition, there was a soft, rumbling, diastolic murmur over the mitral area. There was no fullness of the neck veins. There was moderate distention of the abdomen, with generalized tenderness but no ascites. The liver edge was felt at about the level of the umbilicus and was firm although no nodules were noted. There was a poorly defined mass, 3 to 5 cm., in the right lower quadrant

TABLE I
LABORATORY DATA OF THREE PERIODS DURING THE PATIENT'S ILLNESS

Data	Normal	First Admission	Second Admission	Terminal
Albumin (gm. %)	4.0–5.2	2.9	2.6	2.3
Calcium (mg. %)	9.0–10.5	8.0	7.9	9.6*
Prothrombin time (sec.)	14	16.6	16.2	14.7*
Carotene (mg. %)	.06–1.2	.01	.03	.....
Cholesterol (mg. %)	150–250	112.0	80.0	81.0
Alkaline phosphatase (Bodansky units)	2.0–4.0	4.3	5.9	8.0
Potassium (mEq./L.)	3.5–5.7	4.2	3.3	4.1
Fasting blood sugar (mg. %)	70–90	84.0	65.0	.....
Triolein-I^{131} study (% in 72-hr. stool)	0–3	.....	23.0	.....
Schilling test (% in 48-hr. urine)	>3	.....	1.3	.....
5-Hydroxyindolacetic acid (mg./24 hr.)	1.7–5.5	.....	384 and 635	.....

* Maintained on parental calcium and vitamin K.

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FIG. 1. Four-hour roentgenogram of a small bowel series showing rigid loops of ileum and mucosal irregularities.

of the abdomen. Proctoscopic examination was within normal limits.

The laboratory data are summarized in Table I. The hemoglobin was 11.6 gm. per cent; the red blood cell count, 4,000,000 per cu. mm.; and the hematocrit, 34.5 per cent. The white blood cell count was 7,400 per cu. mm. with 65 polymorphonuclear cells and 10 band forms, 19 lymphocytes, 2 monocytes, 2 eosinophils and 1 basophil. The erythrocyte sedimentation rate (Wintrobe) was 50 mm. Cultures of the blood and peritoneal fluid were negative. The screening test for urinary 5-hydroxyindoleacetic acid [6] was also negative.

Pertinent radiologic studies revealed a slightly enlarged heart in the transverse diameter. The barium enema and upper gastrointestinal series were within normal limits; however, the small bowel examination showed a markedly abnormal pattern with several loops of ileum showing shaggy, irregular mucosal borders and others showing narrowing and dilatation. (Fig. 1.) The radiological interpretation was advanced regional enteritis.

The patient had a daily low-grade fever with peaks in temperature of 39.5°C. At the end of the first week of hospitalization she passed a bloody stool, became acutely ill and showed signs of small bowel obstruction. On May 7, 1957, Dr. Richard Karl performed

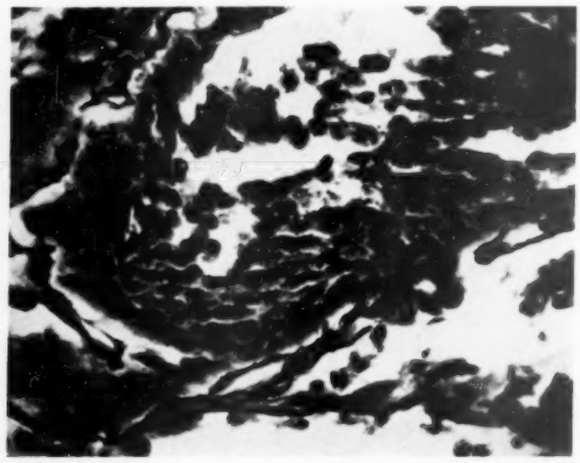


FIG. 2. Photomicrograph of metastatic nodule demonstrating argentaffin cells. Original magnification × 640.

laparotomy and found ascites, a constricting lesion in the mid-ileum and a cyanotic, dilated loop of adjacent bowel. In addition, he noted numerous metastatic nodules, one of which caused obstruction to the venous drainage of the compromised bowel. One-hundred ten centimeters of mid-ileum was resected and an omental nodule was biopsied. (Fig. 2.) The pathology report was carcinoid tumor and infarction of the ileum. Postoperatively the patient noted several episodes of "plum-red" flushing of the face and upper thorax. Three days after operation 25 mg. of the benzyl analog of serotonin (BAS)* and an anticholinergic drug, Trasentine,® 75 mg., were administered orally three times daily. During one month of this therapy she experienced no diarrhea and only rare facial flushing. In June 1957, she discontinued all drugs and noted gradually increasing abdominal girth, anorexia and wasting of her limbs. Oral diuretics were ineffective and in August 1957, three months after operation, intermittent episodes of watery diarrhea recurred and pedal edema appeared. The stools were extremely foul-smelling but contained no blood. Her symptoms progressed and were accompanied by occasional flushes similar to those observed in the hospital. When she became bedridden, she returned for readmission to The New York Hospital.

On admission December 27, 1957, the patient was chronically ill and poorly nourished. The temperature was 37°C., pulse 100, respirations 16, and blood pressure 115/75 mm. Hg. Significant physical findings included facial and thoracic telangiectasia without spider angiomas; marked protuberance of the abdomen with a prominent fluid wave and shifting dullness; moderate pitting edema of the legs and sacrum; and a trophic ulcer on the right heel. Examination of the heart was unchanged from the previous admis-

* Generously provided by Dr. D. W. Wooley of The Rockefeller Institute, New York, New York.



FIG. 3. Photomicrograph of ileal mesentery showing tumor cells, dilated venules and lacteals. Hematoxylin and eosin. Original magnification × 65.

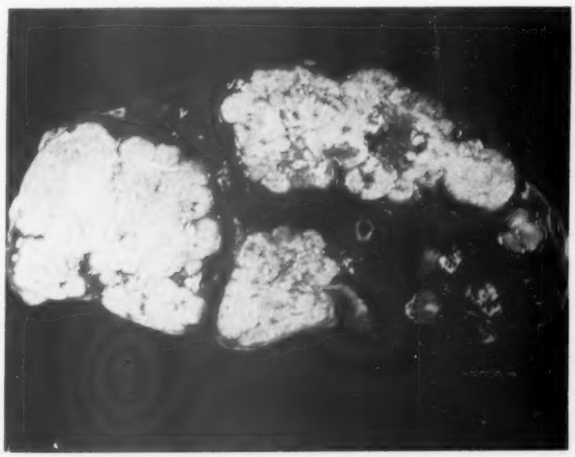


FIG. 4. A section through the enlarged liver showing large metastatic nodules.

sion and the lungs were clear to percussion and auscultation.

The initial laboratory data included a normal urinalysis, white blood cell count, and differential. The hemoglobin was 11 gm. per cent, the red blood cell count, 4,000,000 per cu. mm.; and the hematocrit 34.5 per cent. Significant chemical studies (Table 1) included serum albumin, 2.9 gm. per cent; calcium, 8.0 mg. per cent; carotene, 0.01 mg. per cent; cholesterol, 112 mg. per cent; and a prothrombin time of 16.6 seconds. Results of serum bilirubin, transaminase, thymol turbidity and cephalin flocculation tests were all normal. Results of stool guaiac tests were negative.

Because the venous pressure (brachial vein) was 140 mm. of saline solution and the circulation time was nineteen seconds (sodium succinate), the patient received 1.2 mg. of digitoxin on the fourth hospital day and a daily maintenance dose of 0.1 mg. thereafter. After the administration of 25 gm. of salt-poor albumin, two paracenteses yielded 8,000 ml. of clear fluid with a total protein content of 2.1 gm. per cent and a specific gravity of 1.012.

The patient's diarrhea, her major hospital symptom, remained refractory to anticholinergic drugs and Kaopectate®. A gluten-gliadin-free diet for a period of one week had no effect on the frequency or character of the stools. A repeat trial of the benzyl analog of serotonin, 25 mg. three times daily, also failed to affect the diarrhea. The most effective agent was tincture of opium, thirty drops daily in divided dosage. Her condition improved initially on a regimen of supplemental potassium, calcium chloride, mercurial diuretics, multiple vitamin supplements and a low salt diet. Although she ingested 1,800 calories daily and had a gradual diuresis of 60 pounds, she deteriorated progressively and died in a markedly cachectic state on the 104th hospital day.

At autopsy the body weighed 33 kg. and was wasted. The peritoneal cavity contained 5,000 ml. of serous fluid and several tumor nodules, 1 cm. in size, in the pelvis and periportal and peripancreatic lymph nodes. The ileal anastomosis was adherent to a tumor mass in the mesentery but the remainder of the bowel was uninvolved. The portion of ileal mesentery containing tumor showed dilated lacteals and venules (Fig. 3); however, the blood and lymph vessels of the entire jejunum appeared normal. Large segments of the liver were replaced with tumor. (Fig. 4.) The heart weighed 155 gm. On section the myocardium was dark brown and glistening. Mitral stenosis and insufficiency were present, with thickened leaflets and shortened, fused chordae tendinae. The cross-sectional area of the mitral valve was estimated to be 2 to 3 square cm. In addition, the aortic and tricuspid valve leaflets were slightly thickened and some tricuspid chordae tendinae were shortened and thickened. An incidental finding was an anomalous pulmonary valve with four delicate cusps. Microscopically, some calcification was found in the mitral and aortic valve which were thickened by collagenous and elastic fibers. There was some vascularization of the mitral valve. These cardiac findings appeared to be quite consistent with rheumatic heart disease rather than with carcinoid fibrostenosis as described by MacDonald and Robbins [7]. Incidental findings included osteoporosis of the cancellous bone, a 2 cm. thyroid adenoma and a uterine myoma. The pancreas, lungs and kidneys revealed no abnormalities.

COMMENTS

Although steatorrhea is alleged to occur in association with any prolonged diarrheal state [*8–10*], it has not been described in the malignant carcinoid syndrome. In this patient the fecal excretion of 23 per cent of ingested I^{131}-labeled triolein and the low serum concentration of calcium, prothrombin, albumin and cholesterol

reflect severe malabsorption, particularly of fat. The evidence for intact liver function in this patient precludes the possibility that the abnormalities of the albumin, cholesterol and prothrombin were due to malfunction of this organ. Poor absorption of Co^{60} B_{12} (Schilling) might be explained in part by the loss of one single small specimen late in the second day of the collection; however, this possibility does not seem likely.

Although the pathogenesis of this state is not clear, there are several possible explanations. Edema of the bowel wall associated with the marked ascites and hypoalbuminemia might have been a contributing factor in this patient's diarrhea; however, it is doubtful that these factors should be assigned an important role. That the diarrhea and steatorrhea were due to the resection of 110 cm. of ileum is unlikely in view of the studies of intestinal absorption in patients who have undergone far more extensive resections without subsequent significant impairment of absorption [*11,12*]. Furthermore, there was evidence of malabsorption prior to the resection of her ileum. (Table 1.)

Since a prominent symptom of pellagra is diarrhea, it is possible that impairment of niacin metabolism in patients with metastatic carcinoid is a contributing cause. Niacin deficiency accompanying the carcinoid syndrome, postulated in recent reviews [*1,13*], has been demonstrated by Sjoerdsma et al. [*4*]. Nicotinamide, 150 mg. per day, was given orally to our patient for twenty-two days without demonstrable effect on the diarrhea. The possibility of inadequate absorption of this substance exists; however, failure to respond to the inordinately large dosage administered makes this an unlikely explanation. Other symptoms of severe niacin deficiency such as stomatitis, neuritis and cerebral aberrations were not present in this woman although skin lesions and mild glossitis suggestive of pellagra were noted. No N-methyl nicotinamide urinary excretion studies were performed.

Since tumor was found to have invaded the mesentery of the small bowel, it is possible that lymphatic obstruction might have contributed to the steatorrhea. The mechanism would be the same as that in tabes mesenterica and lymphoma of the small bowel, both of which are associated with the malabsorption syndrome [*14*]. However, at postmortem examination only a limited section of ileal mesentery was involved with tumor and the entire jejunal mesentery was free. With this amount of normal bowel, such a mechanism can be assigned only a limited pathogenetic role in the clinical picture.

Perhaps the most reasonable explanation for the diarrhea and steatorrhea should be sought in the effect of excessive amounts of 5-hydroxytryptamine upon the intestine. Experimentally, hypermotility of the intestine has been produced in both man and animals following administration of this substance [*15–17*]. Although no circulating levels of 5-hydroxytryptamine were obtained in this patient, elevated urinary levels of 5-hydroxyindoleacetic acid certainly indicate increased amounts of its precursor, 5-hydroxytryptamine, in the blood [*18*].

Regardless of the basis for steatorrhea, it seems certain that defects in absorption in our patient contributed significantly to the malnourished state and it is therefore possible that malabsorption, particularly of fat, may help to explain the clinical picture seen in other patients with the metastatic carcinoid syndrome.

Regarding the ineffectiveness of the benzyl analog of serotonin in the therapy of this patient: Although this material may inhibit the action of 5-hydroxytryptamine upon the intestine of dogs, an extremely large dosage, 0.1 mg./kg., given intra-arterially was necessary, 1.0 to 3.0 mg./kg. intravenously having been found impotent [*16*]. In our patient the BAS dosage may have been insufficient.

SUMMARY

The clinical and postmortem findings in a patient with metastatic carcinoid tumor and a severe malabsorption syndrome are presented.

Of the possible mechanisms for steatorrhea in this patient, the effect on the intestine of circulating 5-hydroxytryptamine is considered most likely. It is suggested that the cachexia, hypoproteinemia and other deficiencies commonly seen in the metastatic carcinoid syndrome may be due in part to steatorrhea and malabsorption.

Acknowledgment: We are grateful to Dr. Bry Benjamin for his interest and permission to study his patient. We are also indebted to Drs. G. E. Murphy and W. Campbell of the Department of Pathology, Cornell University Medical College, for the pathological data and interpretation, and to Dr. D. W. Wooley of The Rockefeller Institute, who generously provided the BAS used in this study.

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"Stiff-Man" Syndrome*

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ALTHOUGH Ornsteen [*1*] described the first "stiff-man" in 1935, new interest [*2–7*] in this bizarre affliction has been aroused by Moersch and Woltman [*8*]. The syndrome is characterized by the insidious onset of progressive rigidity of skeletal muscle with variable episodes of muscular spasm.

Whether this is fundamentally a disease of muscle, collagen, or nervous tissue is still unknown. Recent work has suggested a metabolic defect in such patients. It is hoped that the following case report with multiple studies will add to the growing interest in this peculiar illness.

CASE REPORT

A. H. is a twenty-eight year old married Negro man who was admitted to the Durham Veterans Administration Hospital in October 1954 with a chief complaint of progressive stiffness of the neck for one and a half years. While in the Army in 1952 he had fallen from a truck and sustained several minor abrasions on his forehead. He had no immediate sequelae and was asymptomatic until four months later. In February 1953 prior to his discharge from the service he noted tenderness and soreness in his neck. Limitation of motion was minimal, and a diagnosis of traumatic arthritis was made. Despite the insidious but progressive stiffness in his neck he did well until several months prior to admission when mild soreness recurred in his shoulder muscles. Although the rigidity of his neck muscles fluctuated from day to day he never had severe spasms. The patient denied skin changes and any family history of neuromuscular disease or diabetes mellitus.

General physical examination including vital signs was normal except for the neuromuscular examination. All voluntary cervical muscle groups were noted to be stony hard, non-tender, and immobile. He was unable to move his neck in any direction. There was minimal atrophy and early limitation of motion in the trapezii and paraspinal muscles bilaterally. At that time the patient had almost complete range of motion in his arms. The neurological examination, including deep tendon reflexes, was normal. There were no abnormal skin changes or fasciculations.

Routine laboratory studies including hemoglobin, serum serology, stool for occult blood, x-ray films of the chest, cervical spine and lumbosacral spine were

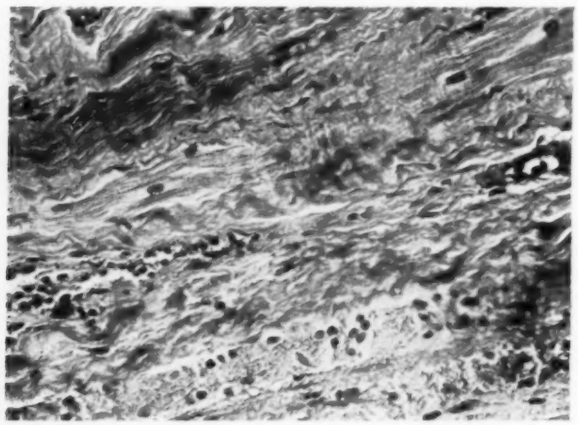


FIG. 1. October 1954. Right sternocleidomastoid muscle. More normal cross striated muscle fibers are present at the top, increased connective tissue and some inflammatory cells at center and a fragmented muscle fiber at the bottom. Original magnification × 20.

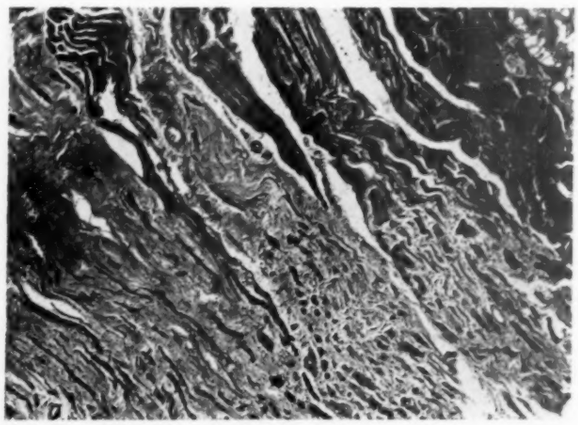


FIG. 2. October 1954. Right sternocleidomastoid muscle. Note bundle of normal muscle fibers at upper right with increasing loss of muscle fibers with replacement of connective tissue at lower left. Original magnification × 10.

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FIG. 3. May 1957. Note the upturned face and the abducted arms. This is the patient's resting position.

normal. The white blood cell count was 4,350 per cu. mm. with a normal differential except for 4 eosinophils.

Biopsy of the right sternocleidomastoid muscle revealed dense hyalinized connective tissue separating atrophied muscle bundles. There were foci of sarcolemmal hyperplasia, and areas with loss of muscle striations. (Figs. 1 and 2.)

A cervical myelogram was within normal limits. Under sodium pentothal anesthesia and intravenous succinylcholine chloride, the neck muscles remained rigid and immobile, despite flaccidity in all other muscles. The patient received no benefit from physiotherapy.

In August 1955 the patient was admitted to the Richmond Veterans Administration Hospital. The history and physical examination were as before except for increased rigidity in the left shoulder. Again routine laboratory studies were unremarkable except for a persistent leukopenia (white blood cell count 3,700 to 1,600 per cu. mm.) with a persistent mild eosinophilia on differential smear. After some residual Pantopaque® was removed from the cervical canal,

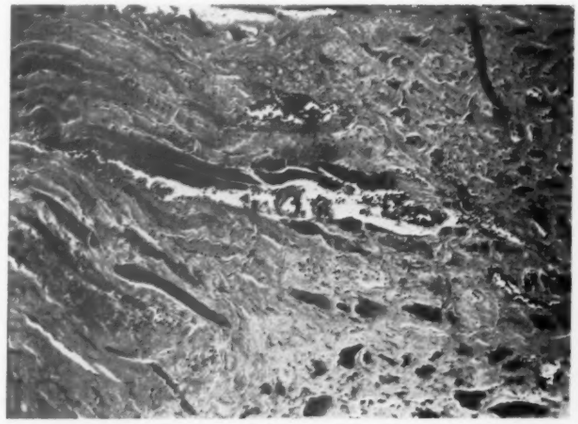


FIG. 4. May 1957. A section of trapezius muscle showing the marked fibrous replacement of muscle and sarcolemmal cell proliferation at center and right. Original magnification × 2.5.

the patient was placed in halter traction for two and a half months and a cervical brace for one month with little, if any, improvement.

In March 1956 he was again admitted to the Richmond Veterans Administration Hospital because of progression of his disability. His head was now completely immobile in a slightly forward upturned position. There was bilateral elevation of the shoulder girdles. The cervical, intercostal, and paraspinal muscles were rigid, hard, and immobile. Laboratory values continued to be normal except for the leukopenia and mild eosinophilia. Sedimentation rate was normal repeatedly. Serum creatinine was 1.7 mg. per cent.

Because of the patient's blunted affect and the possibility that this could represent a functional illness, a complete psychological examination (including WAIS, Bender-Gestalt, Rorschach, and Szondi tests) was carried out. It was concluded that the patient's thinking was repetitive and stereotyped. His responses indicated marked dependency with intense sadistic impulses. There was no evidence, however, of psychosis.

Again, general anesthesia with intravenous succinylcholine chloride failed to produce relaxation of the involved muscles. Muscle biopsy was also consistent with atrophy and fibrosis. The patient received no benefit from a sixteen day course of phenylbutazone (total of 6,000 mg.), intravenous mephenesin. and 600 r radiation to the neck.

In May 1957 he was admitted to the Durham Veterans Administration Hospital for the second time. Again the history of progressive rigidity with minor fluctuations in stiffness was obtained. Physical examination revealed further increase in rigidity. (Fig. 3.) He sat with his head hunched forward and face turned upward, forced by the immobile rock-like trunk muscles to pivot his entire body in gazing laterally. His arms were held in a permanent position of partial flexion and abduction. There was minimal

TABLE 1
ORAL GLUCOSE TOLERANCE TEST

Time (min.)	Blood Sugar (mg./100 ml.)	Urine Sugar (Clinitest®)	Serum Phosphorus (mg./100 ml.)
0	68	0	3.42
30	135	0	3.33
60	138	4+	2.77
90	168	4+	2.79
120	110	4+	2.74
150	114	Trace	2.81
180	112	0	2.88
210	108	0	3.10
240	100	0	3.31

involvement of the leg muscles. Neurological examination was normal except for the muscle changes.

Laboratory studies including hemoglobin, hematocrit, sedimentation rate, serum serology, urinalysis, stool examination, agglutinations for typhoid, paratyphoid and brucella, complete blood electrolytes, cholesterol, total protein, basal metabolic rate, rheumatoid hemagglutination titer, radioactive iodine uptake, electrocardiogram, electroencephalogram, antistreptolysin titer and C-reactive protein were repeatedly normal. Plasma electrophoresis revealed an albumin of 3.7 mg. per cent and a globulin of 3.2 mg. per cent with a slight decrease in $alpha_2$ globulin and a $beta_2$ globulin band. Pulmonary function studies disclosed a marked decrease in vital capacity and maximum breathing capacity. Blood gas studies revealed an elevated pCO_2, normal O_2 saturation, and a decreased sensitivity of the respiratory center. Electromyography showed occasional spotty weak motor units and no response to electrical stimulation over the involved musculature. The uninvolved muscle had a normal record. A muscle biopsy specimen (Fig. 4) showed almost complete replacement of muscle with fibrous tissue.

The leukopenia was persistent. Bone marrow examination, chromium tagged red blood cell survival times and L.E. cell preparations were within normal limits. Twenty-four hour creatine excretion was normal. Total serum hexosamine and seromucoid hexosamine were normal. A glucose tolerance test revealed an elevated two hour blood sugar and the presence of a reducing substance in the urine. Physiotherapy was of little value.

In May 1958 the patient's condition was reevaluated. There had been little change in his rigidity. Multiple studies including a serum glutamic oxalacetic transaminase were normal. Another twenty-four hour creatine excretion was slightly elevated (139 mg./twenty-four hours). An oral glucose tolerance test with simultaneous measurement of serum phosphorus levels was carried out. (Table 1.) The blood glucose curve was normal and was accompanied by the expected reciprocal fall in serum phosphorus. Despite the normal glucose tolerance curve, the patient spilled 4 plus amounts of glucose at one, two, and two and one-half hours after administration of glucose. Analysis of the reducing substance in the urine by both enzyme reaction and chromatography [*9*] revealed large amounts of glucose.

COMMENTS

Although Ornsteen [*1*] believed his patient to have fibromyositis, this was the first of nineteen cases of the "stiff-man" syndrome. Many of the reports are far from complete, making a careful correlation of data difficult.

The most striking feature in all cases has been the board-like rigidity of involved muscle. While Moersch and Woltman [*8*] noted the onset of illness in the trunk or neck muscles in the majority of their fourteen cases, in a recent patient [*6*] a dislocated thumb was the first manifestation of the syndrome. The occurrence of dramatic prolonged muscle spasm is a common but not invariable feature. The contractions may last for days and have been severe enough to bend Smith-Petersen nails in two patients [*3,5*]. The disease is predominately one of males, but several females have been afflicted [*3,8*]. There has been no well documented precipitating event or family history. Although our patient noted the previously described insidious onset in neck and trunk muscles, he was not plagued by severe spasms.

As in our case, multiple laboratory studies have been of little value in elucidating the etiology of this illness. This is the first report of an associated leukopenia. The one recurrent abnormality noted in six earlier cases [*3,6,8*] was the presence of a reducing substance in the urine. It is a matter of conjecture as to whether or not the majority of the reducing substances noted in previous cases is glucose, as it was in our case. Price and Allott [*6*] measured the serum phosphorus and potassium after administration of pyruvate, glucose, glucose with insulin, and epinephrine. They were surprised to find a consistent rise in serum phosphorus and a fall in serum potassium in all four experiments. While their patient had a normal glucose tolerance curve, he was noted to have a reducing substance in his urine on random sampling. Preliminary observations also suggested a period of sodium retention, prior to, and sodium diuresis, after a severe spasm. In view of the second normal glucose tolerance test, our patient's initial abnormal test may have been a reflection of poor carbohydrate intake prior to the test. The proved glycosuria would suggest a decreased

tubular reabsorption of glucose. Serum glutamic oxalacetic transaminase values have not been previously reported. The normal level in this patient presumably indicates that there is no active necrosis of muscle at this time.

Since only five muscle biopsies [*3,6,8*] have been reported, final evaluation of the pathologic condition of the muscle must be delayed. In three patients [*6,8*] the muscle appeared normal. Ornsteen [*1*] noted that the subcutaneous tissue had a marked increase in fibrous elements. Although most of the muscle appeared normal, there were areas of muscle degeneration and sarcolemmal hyperplasia. In reporting on a woman who died with "stiff-man" syndrome, Asher [*3*] described abnormal variations in size and staining reaction of muscle, a marked increase in collagen and elastic tissue, and areas of nuclear aggregates and lymphorrages. The most striking feature in our biopsy specimens was the massive infiltration of collagen fibers. In early biopsy specimens there was loss of striation and sarcolemmal hyperplasia, but no cellular infiltration or abnormality of blood vessels. As in our case several authors have noted no pathognomonic changes in the electromyogram.

In view of our present meager knowledge of this syndrome, it is difficult to classify the disease, much less define the etiology. The possibility that this clinical picture represented a conversion reaction was entertained in our case as well as in many of the previous cases. This seems to be a very remote possibility. Although syphilitic myositis, local tetanus, and dystonia musculorum deformans [*2*] have been mentioned in the differential diagnosis, these seem unlikely. Moersch and Woltman [*8*] speculated on the role of the central nervous system and basal ganglia in this disease, which they believed to be a metabolic disorder. The demonstration of abnormal phosphate metabolism in one patient and the recurrence of a reducing substance in the urine of many such patients would lend support to the concept of a metabolic defect.

Price and Allott [*6*] suggested that this was either a new disease or a variant of a previously described entity. The insidious progressive muscular rigidity, absence of systemic symptoms, and normal neurological examination are consistent findings in myositis fibrosa (myositis fibrosa generalisata, primary generalized myositis fibrosa, or fibromyositis) as well as the "stiff-man" syndrome. Myositis fibrosa as described by Janicke [*10*], Burton [*11*], Blau [*12*], Somers [*13*], Stewart and Macgregor [*14*], however, was not accompanied by muscle spasms. It is of interest that Somers [*13*] in 1939 suggested a metabolic origin for myositis fibrosa. Recently, myositis fibrosa has been considered a variant of dermatomyositis [*15*]; and this may be true of the "stiff-man" syndrome as well.

Innumerable forms of treatment have had little discernible effect on the disease process.

SUMMARY

A case of "stiff-man" syndrome is reported in which the salient features are progressive muscular rigidity, leukopenia and glycosuria.

With our present knowledge, it is impossible to classify this rare disorder, although there is some evidence to suggest an underlying metabolic defect.

Acknowledgment: The authors wish to thank Dr. A. G. Smith for his careful review of the muscle biopsy specimens.

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Hereditary Ectodermal Dysplasia of the Anhidrotic Type Associated with Primary Hypogonadism*

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IN his book "The Variations of Animals and Plants under Domestication," Charles Darwin [*1*] describes a family in India, reported to him by Widderburn in 1838, that was afflicted with defective teeth and inability to sweat properly. This was the first recording of the anhidrotic type of ectodermal dysplasia, an inherited disorder characterized by defective development of the teeth, hair, sebaceous glands and sweat glands. The first report of this syndrome to appear in the medical literature was by Thurman [*2*] in 1848, and Guilford [*3*], a dentist, reported the first American case in 1883. In 1929, some ninety-one years after the first report, Weech [*4*] reviewed the subject and at that time only ten cases of this rare disorder had been described. At the present time approximately 100 of these cases have been reported and the disorder has been reviewed by a number of authors [*5–8*].

Many defects have been described in association with this syndrome, such as absent tears [*2*], absent breast tissue [*7,9–11*], mental retardation [*12–14*], cataracts [*13,14*], deformed nails [*13–15*], neurolabyrinthitis [*15*], syndactyly, absent toes [*16*], anemia [*17*], and vascular purpura [*18*]. These defects have been found in only a few instances whereas a saddle nose deformity, atrophic rhinitis and palmar and plantar hyperkeratosis were present in most of the cases. The association with established primary hypogonadism has not previously been described.

CASE REPORTS

CASE I. L. W. (UVH No. 435097), a twenty year old white high school graduate, was admitted to the University of Virginia Hospital on August 8, 1957, for evaluation of hypogonadism. The patient apparently was the product of a normal pregnancy and delivery, and appeared normal at birth with a normal amount of scalp hair. At approximately six months of age the mother noted that his skin was dry and smooth with no hair. She also observed that he was unable to sweat. His nose was deformed and he was troubled by a chronic rhinitis. It was noted that his teeth were of "poor enamel" and he began losing them at the age of six. There was complete loss of teeth by the age of thirteen. Although he complained of heat intolerance, this was not marked unless he exerted himself in a warm environment. On one occasion, while cutting wheat on a hot day, he collapsed and was revived when taken to a cool place and sponged with water. He stated that he had never noticed any sweat on his skin except in the areas in front of his ears, the axillae, and palms of the hand. He also noted that he had not developed sexually. His penis had remained small, he had noted no testicles or pubic hair, and his voice remained high pitched. He said that he had had penile erections but never an ejaculation.

At the age of six the patient had an episode of acute arthritis with a swollen left ankle and later swelling and tenderness of the toes on the same side. He was told that this was rheumatic fever but he apparently had no fever or cardiac signs at the time. He had had three similar episodes of an acutely painful swollen joint involving either the knee, ankle or great toe, usually only one joint at a time, and lasting about one week.

The patient is one of five boys. Two of his brothers have not been observed to have any of the stigmas of the syndrome. One of his brothers, E. W., has a similar condition and is reported as Case II. Another brother died at the age of six of a kidney infection and according to the mother his skin and facial appearance were similar to his affected brothers. One of the patient's paternal first cousins, a girl twenty-two years of age, has skin similar to the patient's but does not have the saddle nose deformity and has normal

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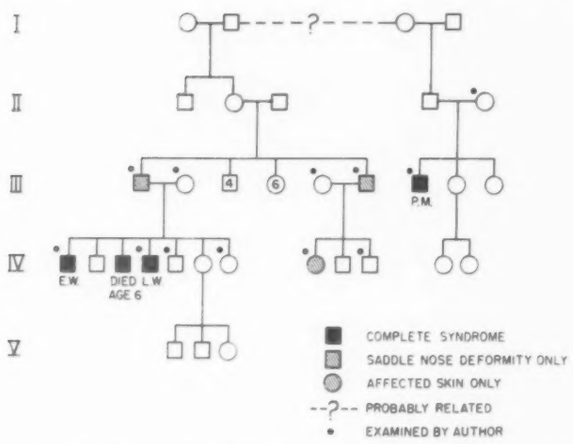


FIG. 1. Pedigree of L. W. (Case I), E. W. (Case II), and P. M. who lived in a neighboring town and was probably related. Symbols are numbered from left to right for each generation. I: 2 and 3 were both named Hylton lived in the same county of Virginia and although relationship not definitely established were probably related; II: 4 and 5 may represent a consanguineous marriage as families lived in neighboring towns of Virginia; III: 1 and 2, and 5 and 6 may represent consanguineous marriages as families lived in neighboring towns of Virginia; 2 and 5 are first cousins once removed; 3 represents four men who have eighteen children and fifteen grandchildren apparently unaffected; 4 represents six women who have sixteen children and thirteen grandchildren apparently unaffected.



FIG. 2. Case I.

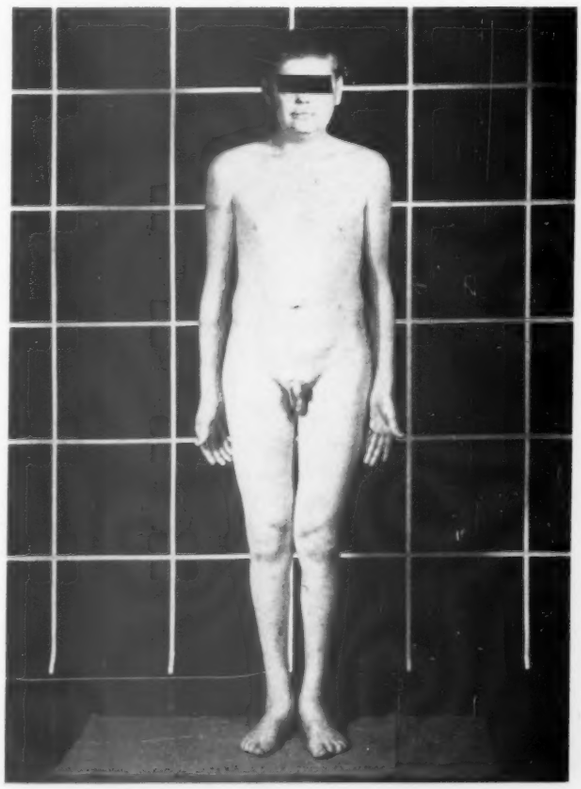


FIG. 3. Case I.

teeth. She also has normal menstrual periods and secondary sexual characteristics. Both this girl's father and the patient's father have depressed nasal bridges giving a saddle nose appearance but have no other features of the syndrome. Also, there is a fifty-eight year old man, P. M., in a neighboring town who has the complete syndrome and who is probably a distant paternal cousin. The pedigree of the patient's family is shown in Figure 1. There was no family history of gout.

On physical examination (Figs. 2 and 3) the temperature was 98.6°F., pulse 68, blood pressure 110/65 mm. Hg, height 62 inches, weight 115 pounds. The patient had a eunuchoid appearance with widening of the hips, female fat distribution, and a high-pitched voice. The arm span was 64 inches, symphysis to floor 34 inches, and symphysis to vertex 29½ inches. There was a marked saddle nose, the supraorbital ridges were prominent, and there was an upward slanting of the eyes giving the face a mongoloid appearance. There was some wrinkling of the skin at the outer margins of the eyes, and the lips were protuberant with a poorly defined vermillion border. The patient was edentulous, wearing upper and lower plates. There were no eye brows, eye lashes, axillary hair, pubic hair or lanugo hair; the only hair present was the scalp hair, which appeared normal. The skin was smooth and dry, and there were scattered areas



FIG. 4. Case II.

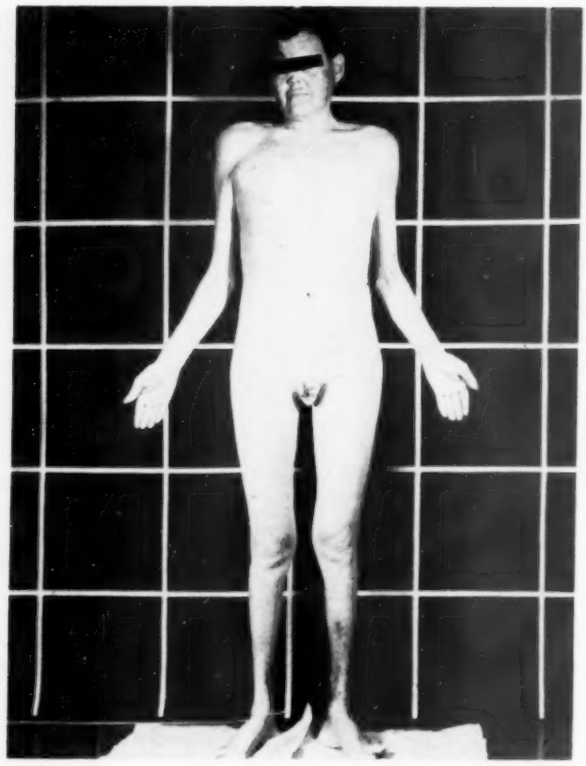


FIG. 5. Case II.

of hyperpigmentation, depigmentation and telangiectases. There was plantar and palmar hyperkeratosis. No sweating was detected in any areas except in front of the ears, the palms of the hand, and the axillae. The nails were normal. Examination of the heart and lungs was normal. On abdominal examination the spleen was palpated 1 fingerbreadth below the left costal region. Examination of the genitalia revealed an infantile penis with phimosis and no palpable testicles. The prostate was prepuberal.

The urine was normal, with a specific gravity of 1.023. The white blood cell count was 5,000 per cu. mm. with 9 band forms, 42 segmented forms, 42 lymphocytes and 7 monocytes. The hematocrit was 46 per cent. The serum sodium, chloride, carbon dioxide, potassium, calcium, phosphorus and alkaline phosphatase were within normal limits. The serum uric acid on admission was 6.2 mg. per cent; on two other occasions, 5.0 mg. per cent and 4.7 mg. per cent. The blood urea was 39 mg. per cent, serum creatinine 2.2 mg. per cent. A phenosulfonphthalein test showed 40 per cent excretion of the dye in fifteen minutes and 70 per cent excretion in two hours. The serological test for syphilis was negative. The basal metabolic rate was −4 per cent, twenty-four-hour radioactive iodine uptake 30.6 per cent, twenty-four-hour 17-ketosteroid excretion in the urine 7.8 mg. (normal range for males, 10 to 25 mg.), and twenty-four-hour gonadotropin excretion in the urine positive for 6.6 mouse units, borderline positive for 100 mouse units (normal range >6.6 mouse units and <100 mouse units). An ACTH stimulation test using 25 international units of ACTH over a four-hour period showed a resting plasma 17-hydroxycorticoid level of 19.6 μg. per cent with a rise to 45.2 μg. per cent after stimulation (normal range, 4 to 32 μg. per cent before stimulation and 35 to 55 μg. per cent after stimulation). Cells from the buccal mucosa as well as from the skin were examined by Dr. Guy Hollifield and found to be of the genetic male type.

Electrocardiogram, intravenous pyelogram and roentgenograms of the chest and skull were normal. An x-ray film survey of various epiphyseal centers showed delayed maturation in that some epiphyses still open would have been expected to have fused by age thirteen. Roentgenograms of the left foot and ankle showed no evidence of gouty arthritis but there was an aseptic necrosis of the distal end of the second metatarsal.

On August 14, 1957, the patient's scrotal contents were explored bilaterally and no testes were found. However, the vas deferens and spermatic cord appeared normal and a biopsy of the epididymis was normal. At the same time a skin biopsy was obtained from the extensor surface of the left forearm which was examined by Dr. Edward P. Cawley, of the Department of Dermatology. Microscopic examination of multiple sections showed only a very occasional sweat gland. Portions of arrector pili muscles were found but no hair follicles or sebaceous glands were seen.

Therapy with fluoxymesterone (Halotestin®) in a dosage of 5.0 mg. a day was prescribed and later increased to 10.0 mg. a day. On this regimen there was a definite increase in strength, well-being and libido. When he was last examined on April 7, 1958,

approximately eight months after the institution of androgen therapy there was a definite increase in the size of his penis and the appearance of a sparse growth of pubic and axillary hair.

The history of episodes of arthritis associated with a variable elevation in the uric acid might suggest the possibility of gout but not enough evidence was available to establish that diagnosis.

CASE II. E. W. (UVH No. 437982), a twenty-eight year old white male printer, brother of Case I, was admitted to the University of Virginia Hospital on October 15, 1957, for evaluation of his skin disorder. The patient gave a history of having marked rhinitis as a child which gradually cleared up as he became older. His teeth had always been "bad" and he lost them all by age eleven. He had heat intolerance and stated that the only areas where he had noticed any sweating were the lateral aspects of his face, the neck, the axillae, and occasionally the palms. He was able to tolerate heat if he was inactive, but the least exertion would cause discomfort. He had also noted that his skin was easily injured and took a long time to heal. He stated that his penis was quite small and that he had noted no testicles or pubic hair. Although he could have a penile erection, he had never experienced an ejaculation. He gave no history of joint symptoms and appeared to be of normal intelligence, having completed the eighth grade.

On physical examination (Figs. 4 and 5) the temperature was 98.6°F., pulse 84, blood pressure 125/70 mm. Hg, weight 115 pounds, height 67½ inches, arm span 69 inches, symphysis to floor 35½ inches, and symphysis to vertex 32 inches. The patient's general appearance was strikingly similar to his brother's. His physical examination was in all respects similar to his brother's except for the following: his spleen was not palpable and he had the additional findings of a lipoma medial to the right elbow, several senile keratoses on the face, areas of dark brown pigmentation and crusting over the anterior tibiae at the sites of superficial abrasions, and a slight pectus excavatum deformity.

The urine was normal, with a specific gravity of 1.014. The hematocrit was 38 per cent with normocytic, normochromic red cell indexes. The white blood cell count was 3,500 per cu. mm. with a normal differential. The blood urea, serum creatinine, uric acid, fasting blood sugar, serum sodium, chlorides, carbon dioxide, potassium, and the phenolsulfonphthalein excretion were all within normal limits. The serological test for syphilis was negative.

The basal metabolic rate was −18 per cent, twenty-four-hour radioactive iodine uptake 30.6 per cent, twenty-four-hour urinary excretion of 17-ketosteroids 14.4 mg., and twenty-four-hour urinary excretion of gonadotropins positive at greater than 100 mouse units. An ACTH stimulation test showed a resting plasma 17-hydroxycorticoid level of 11.9 μg. per cent which rose to 35.1 μg. per cent after stimulation. Cells from the buccal mucosa were of the genetic male type. Roentgenograms of several epiphyses showed delayed maturation with some epiphyses not fused which should have closed by age sixteen.

Fluoxymesterone (Halotestin) was prescribed in a dosage of 5.0 mg. a day which was later increased to 10.0 mg. a day, and when last seen on April 7, 1958, six months after the beginning of this therapy, he had experienced an increase in strength, well-being, and libido and on examination showed a slight but definite increase in the size of his penis and the appearance of a sparse growth of axillary and pubic hairs.

COMMENTS

Hypohidrosis. Weech [*4*] introduced the term "anhidrotic" to describe this type of ectodermal dysplasia, but Felsher's [*19*] suggestion of using the adjective "hypohidrotic" seems more appropriate as most of these patients do not have a complete absence of sweat glands. Upshaw and Montgomery [*7*] as well as Sunderman [*20*] have pointed out that although the exocrine glands may be absent or markedly diminished, the apocrine glands may be normal or even hyperplastic. This point was further confirmed by Felsher using the Minor sweat test and Wagner [*21*] using changes in the electrical resistance of the skin as an indication of active perspiration. Both authors found evidence of sweating over the upper chest and in the axillae. In addition, the two patients Wagner studied showed sweating of the palms, soles and lateral margins of the face, most of these areas being sites of apocrine gland activity. It should be pointed out that sweating was noted in our two patients at similar areas.

Mackee and Andrews [*5*] believed that insensible perspiration was not disturbed in these patients since that function is independent of the sweat glands. This supposition was later supported by Felsher [*19*] who measured the insensible water loss in patients with this syndrome and found that it did not differ significantly from normal subjects. This accounts for the observation that most of these patients, as was true of our two patients, have no difficulty in dissipating heat under ordinary circumstances, but under conditions of increased temperature they become uncomfortable because the reserve mechanism of the active secretion of sweat is not available to them.

Hypogonadism. Although we could find no example in the literature of documented hypogonadism associated with this syndrome, there are several case reports which raise a suspicion

of gonadal hypofunction. Lewin [*22*] reported a forty-five year old chef who had a high-pitched voice and de Silva [*6*] stated that in his patients puberty was delayed until eighteen to twenty years of age and the patients had a high effeminate voice. He raised the question of a gonadal deficiency but also stated that there was hypertrophy of the external genitalia. Falconer [*10*] described a six and a half year old boy with this syndrome and stated that his "genitals are underdeveloped, the testicles being about the size of small cherry stones." In this case the patient had not reached puberty, making it difficult to evaluate his testicular function. Koszewski and Hubbard [*17*] reported the case of a twenty-six year old man who had aplastic anemia associated with this syndrome. At autopsy there was considerable hemosiderosis and the testes were atrophic, but it should be pointed out that testicular atrophy is not uncommon in aplastic anemia especially when there is hemosiderosis [*23*]. It is interesting to note that our second patient had a mild anemia and leukopenia.

There seems little doubt that the two cases described have primary hypogonadism with the classical findings of eunuchoid habitus, delayed skeletal maturation, elevated urinary gonadotropins and response to androgen administration. However, the relationship of the gonadal defect to the ectodermal defect is unclear. The possibility of some intrauterine injury during development should be considered because the hair follicles and tooth germs appear during the eighth to ninth week of fetal life and this is the approximate time that the gonads differentiate from the mesonephros [*24*]. However, this would seem to be unlikely since the sweat glands do not appear until the nineteenth week of fetal life. There is, further, the hereditary pattern of this syndrome, as recorded in the literature and in our cases. The fact that many cases have been reported with mesodermal defects associated with the ectodermal defects of this syndrome [*7,9–11,16*] lends credence to the supposition that one abnormal gene was responsible for the ectodermal and mesodermal (hypogonadism) defects noted in our two patients.

Congenital bilateral anorchism is extremely rare. According to Campbell [*25*] there are only eleven such cases known. It is not certain that the testes were absent in our two patients since the pelvis was not explored to rule out the possibility of undescended testes. However, it seems likely that if testes had been present they would have descended with the spermatic cord, vas deferens and epididymis which were found when the scrotum was explored. On the other hand, in view of the current concept that the external genitalia develop in the female direction in the absence of the male-sex hormone [*26*], it must be assumed that there was some androgenic activity during fetal development. Whether undescended testes or the adrenal glands were responsible for this androgenic activity is open to question.

Heredity. There is no doubt that the anhidrotic type of ectodermal dysplasia is a hereditary disorder. Many pedigrees have been reported in the literature showing affected members in several generations and also several families, such as the one reported here, in which three or more siblings have been affected [*1,9,20,27*]. However, the mode of genetic transmission has been the subject of considerable controversy. The vast majority of the reported cases have followed a sex-linked recessive pattern such as is seen in hemophilia. However, the appearance of the full syndrome in the female, as first reported by Goeckermann [*28*] and later by others [*14,16,21,29*], called for other explanations, since the fathers were apparently unaffected, ruling out the possibility of the affected females being homozygous for the trait. Because of this discrepancy Cockayne [*30*], who reviewed most of the pedigrees up to 1933, thought that there were two types of inheritance, one a sex-linked recessive and the other a dominant. On the other hand, Levit [*31*] thought that all the cases could be explained on the basis of a sex-linked conditionally dominant gene. He used the term "conditionally dominant" to indicate that a pathologic gene might show different degrees of expressivity in a given person or might not be penetrant at all. He thought that this would account for the observation that many women appear unaffected or have an attenuated form of the syndrome while a few have the full syndrome. He also pointed out, as did de Silva [*6*] some years later, that the literature contained no documented instance of a male transmitting the defect to his son or to his son's son. At the present time a review of published pedigrees still reveals no documented example of male to male transmission except for the cases of Helweg-Larson and Ludvigsen [*15*] which showed a simple dominant type of transmission, both sexes and members of each generation being affected. However, these patients

had an associated neurolabyrinthitis and had normal hair and teeth so that the authors were probably describing a different syndrome. Also the pedigrees described by Clarke and McCance [*32*] and by Thannhauser [*33*], while showing primarily a sex-linked recessive pattern, raise the question of male to male transmission in the earlier generations, but the males in question were not personally observed by the authors nor is enough information given concerning them to verify such a possibility.

The pedigree of our patients (Fig. 1) is consistent with three possible modes of genetic transmission: (1) a dominant with incomplete penetrance, (2) a non sex-linked recessive, or (3) a sex-linked recessive. One of the key features of this pedigree is whether the saddle nose deformity noted in the patient's father and one of his paternal uncles is a true *forme fruste* or merely a fortuitous finding. If it is assumed that this nasal deformity is a mild expression of the defect, then the pedigree is an example of transmission of this syndrome from father to son and would be consistent with the observation that P. M., a man in a neighboring town with the syndrome, could be related to our patients through the paternal side of the family. On the other hand, if this were a dominant type of inheritance with incomplete penetrance, it would be unusual to have the other three generations unaffected and to have ten siblings with thirty-four children and twenty-eight grandchildren apparently unaffected.

The second possibility is that the gene was transmitted as a non sex-linked recessive. Since the affected person must get the abnormal gene from both parents in this type of inheritance, this would be more likely to occur if the parents of the affected cases were related. This is a distinct possibility since in each instance the husband and wife came from families who had lived in the same county of Virginia for several generations. However, we were unsuccessful in definitely establishing that these were consanguineous marriages. Kaalund-Jorgensen and Christensen [*34*] reported two brothers with this syndrome whose parents were second cousins and mention that intermarriage is common in the community in India where Widderburn's cases lived. Also one of Upshaw's and Montgomery's patients had consanguineous parents, but these were the only examples of intermarriage that could be found in the literature and Levit [*31*] states that he found the percentage of inbreeding no higher in the parents of patients with this syndrome than in a normal population.

The third possibility is that the saddle nose deformity was not a genetic expression of the syndrome but fortuitous, and the abnormal gene was transmitted by the mother to her sons. This hypothesis is given additional weight by the fact that our patients' mother and the mother of the partially affected girl are first cousins once removed. If a sex-linked recessive type of inheritance is postulated, it must be qualified by saying that it is incompletely recessive in order to account for the partially affected girl. This is the same type of inheritance that Levit [*31*] referred to as conditionally dominant.

SUMMARY

Two cases of hereditary ectodermal dysplasia of the anhidrotic type are described. There was associated primary hypogonadism.

The mode of inheritance of this syndrome is reviewed. It appears that a sex-linked recessive gene which is sometimes incompletely recessive would account for most of the published cases. The pedigree of our patients is compatible with this type of transmission but also could be explained by a dominant gene with incomplete penetrance or by a non-sex-linked recessive gene.

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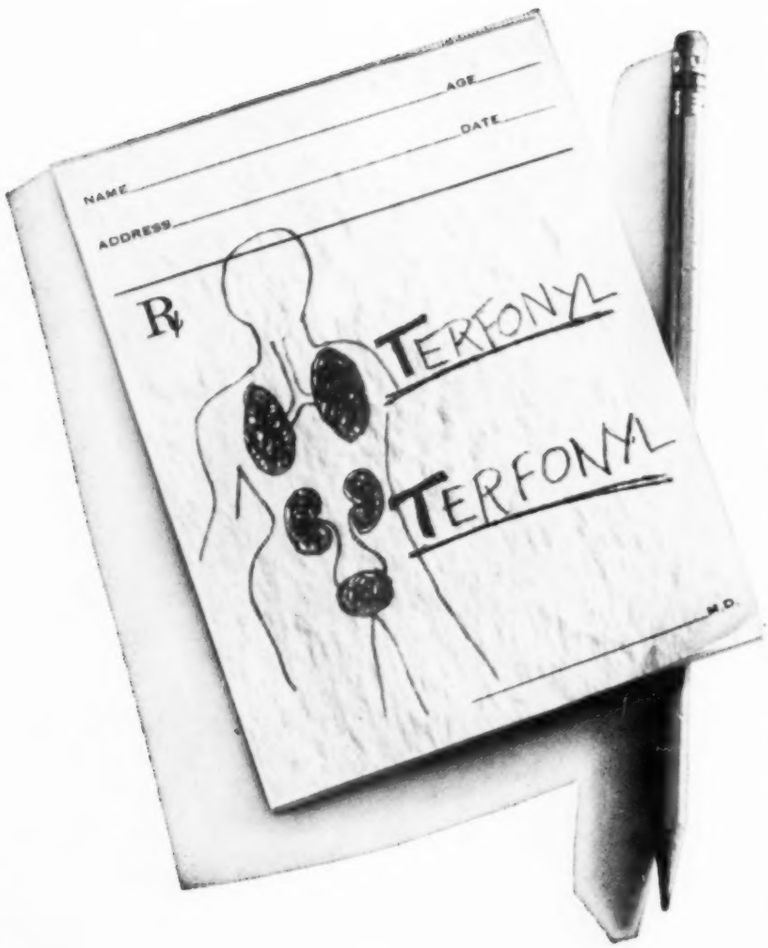
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My back and shoulder were so painful — I called my doctor. He gave me a prescription for some tablets and told me to take one right away.

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ACTS FASTER — usually within 5-15 minutes. **LASTS LONGER** — usually 6 hours or more. **MORE THOROUGH RELIEF** — permits uninterrupted sleep through the night. **RARELY CONSTIPATES** — excellent for chronic or bedridden patients. **VERSATILE** — new "demi" strength permits dosage flexibility to meet each patient's specific needs. PERCODAN-DEMI provides the PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit-forming. Federal law permits oral prescription.

Each PERCODAN* Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. phenacetin, and 32 mg. caffeine.

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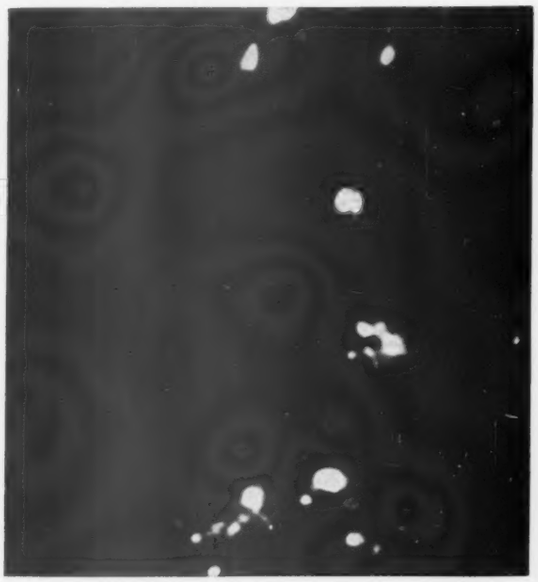
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Clarin* can do this for your postcoronary patients



WITHOUT CLARIN, turbid blood serum five hours after a fat meal: This unretouched dark-field photomicrograph (2500X) shows potentially hazardous fat concentrations circulating in the blood stream of a patient after a standard fat meal.



WITH CLARIN, clear blood serum five hours after a fat meal: After eating a standard fat meal as at left, the same patient has taken one sublingual Clarin tablet. Note marked clearing effect and reduction in massive fat concentrations in this unretouched photomicrograph (2500X).

CLARIN is sublingual heparin potassium. One mint-flavored tablet taken after each meal effectively "causes a marked clarification of postprandial lipemic serum."[1] Clarin facilitates the normal physiologic breakdown of fats, with no effects on the blood-clotting mechanism.[1] It therefore provides important benefits for your postcoronary patients.

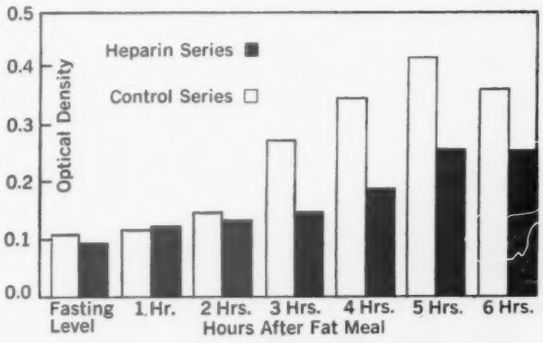
Indication: For the management of hyperlipemia associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

1. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.

2. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959.



Average serum optical density in 36 patients after fat meal with and without sublingual heparin.[2]

*Registered trade mark. Patent applied for.

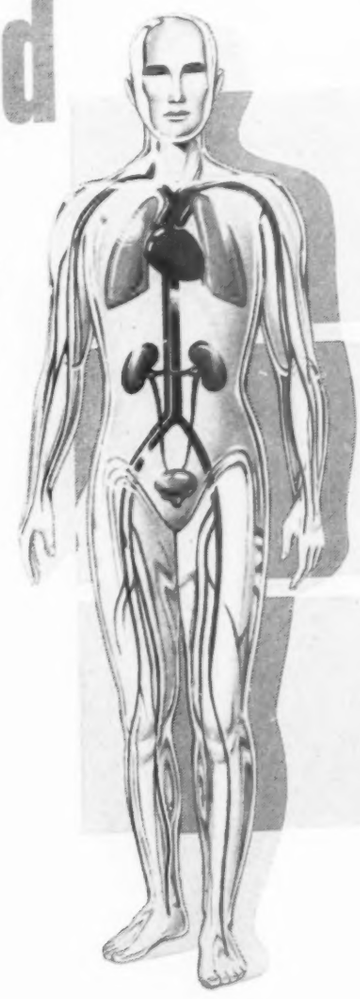
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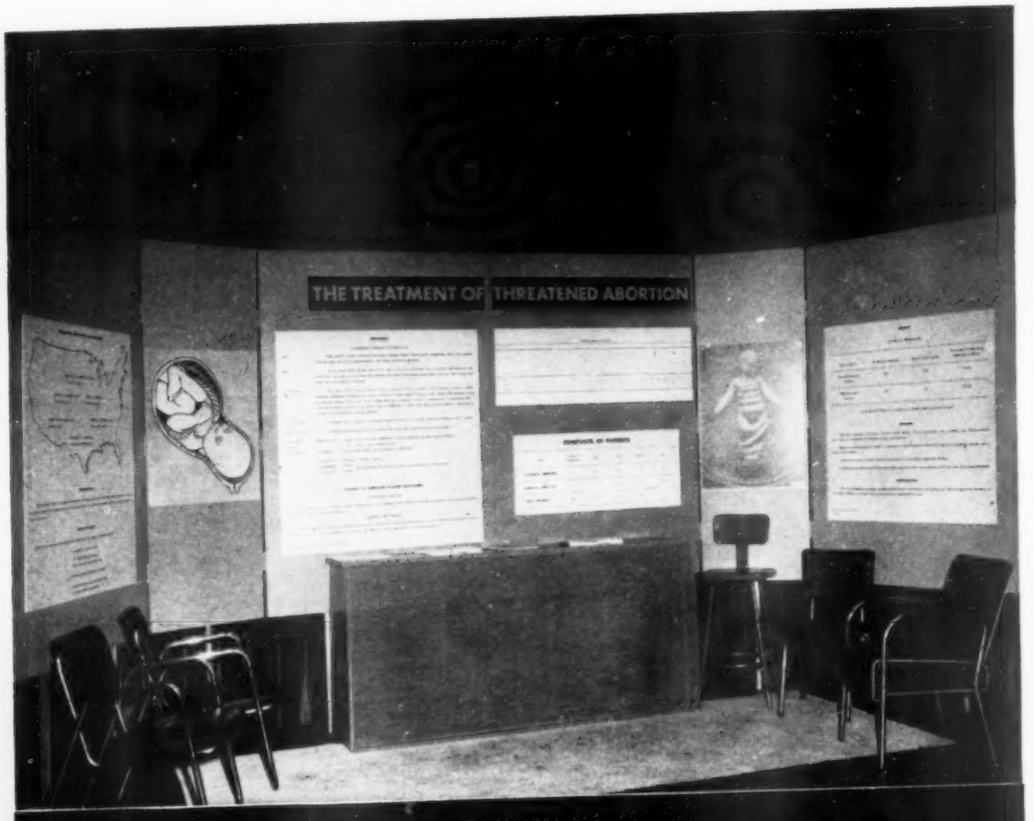
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3 Adjust dosage of all medication: the patient must be frequently observed and careful adjustment of all agents should be made to establish optimal maintenance dosage.

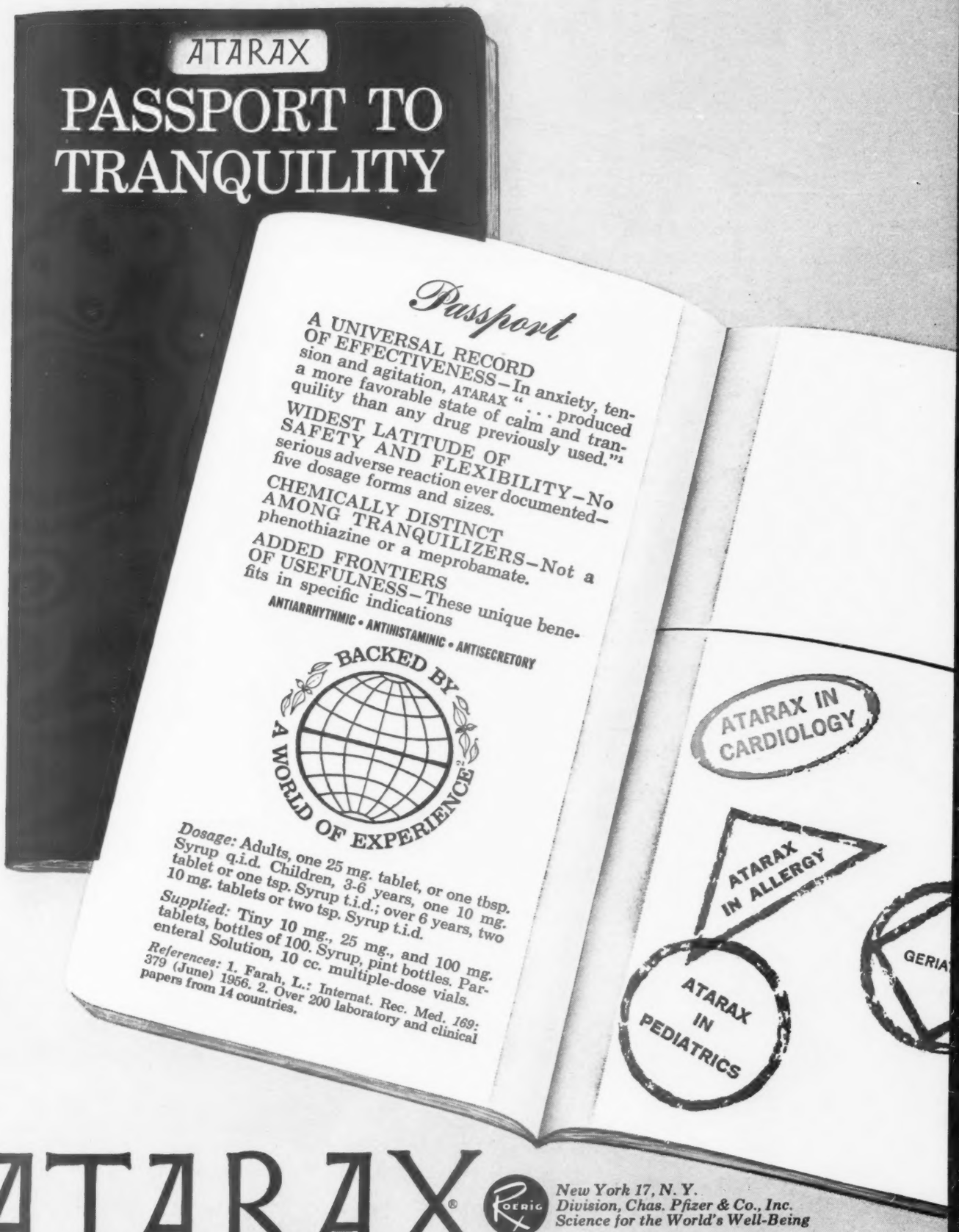
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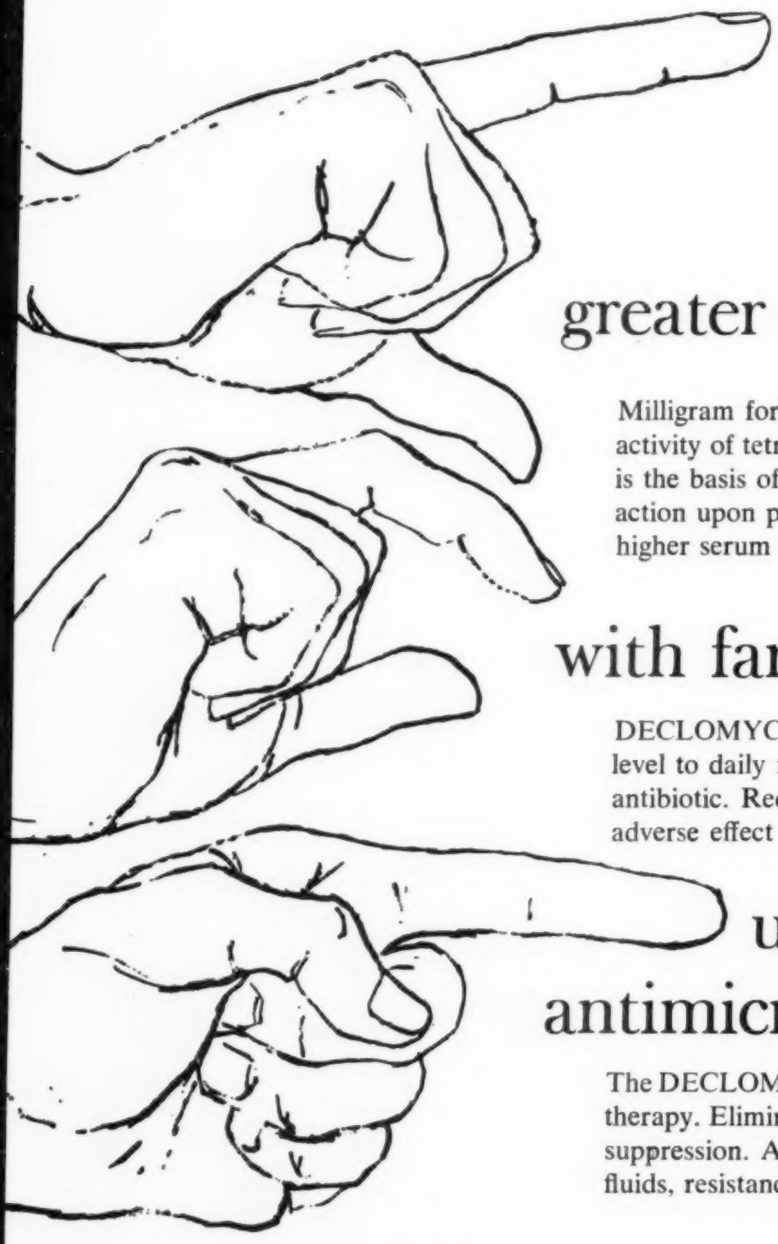
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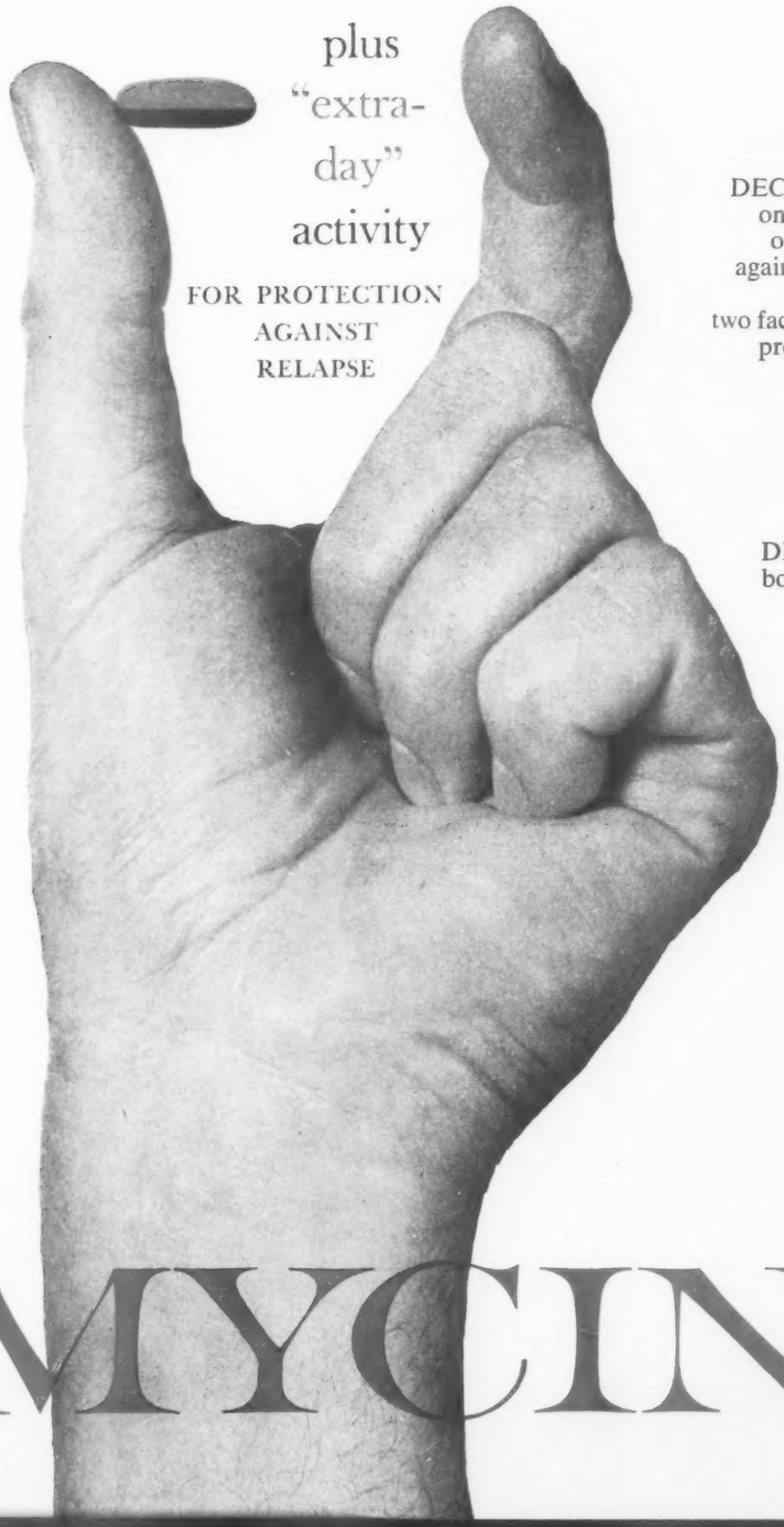
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*Hirsch, H. A., and Finland, M.: *New England J. Med.* 260:1099 (May 28) 1959.

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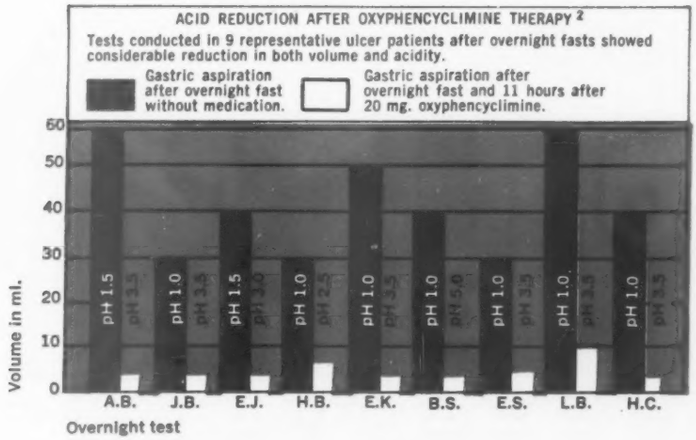
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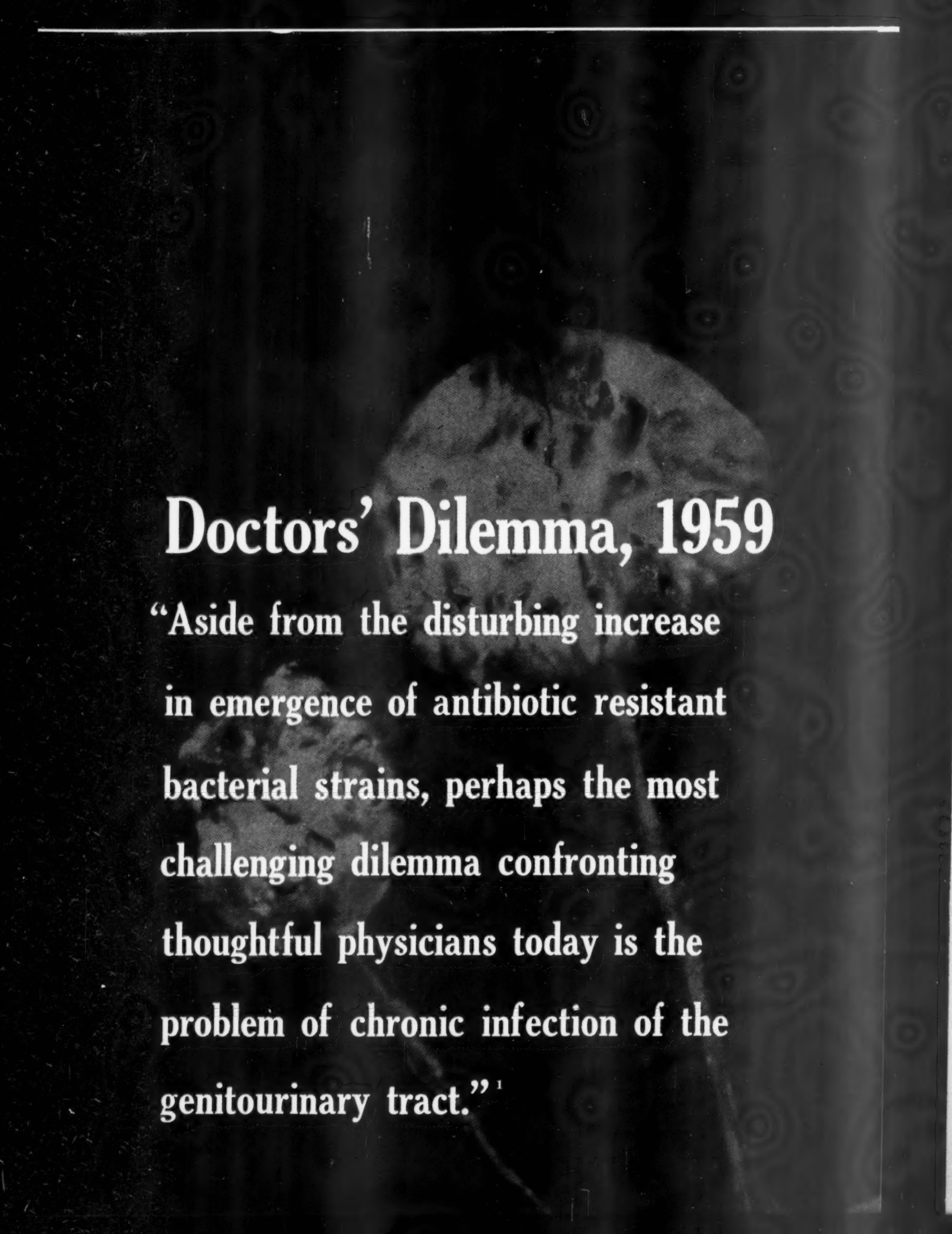
A SENTRY FOR THE G.I. TRACT



References: 1. Steigmann, F.: Study conducted at Cook County Hospital, Chicago, Illinois: In press. 2. Winkelstein, A.: Am. J. Gastroenterol. **32:66** (July) 1959. 3. Data in Roerig Medical Department files. 4. Leming, B. H., Jr.: Clin. Med. **6:423** (Mar.) 1959.

ROERIG

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being



Doctors' Dilemma, 1959

"Aside from the disturbing increase in emergence of antibiotic resistant bacterial strains, perhaps the most challenging dilemma confronting thoughtful physicians today is the problem of chronic infection of the genitourinary tract."[1]

the challenge of chronicity in genitourinary tract infections

"... The physician treating a patient with established chronic urinary tract infection faces a grave problem of management."[2]

to control the chronic case

FURADANTIN®

brand of nitrofurantoin

"... given continuously and safely for as long as three years."[3]

Three recent studies attest to the role of FURADANTIN in the treatment and control of chronic urinary tract infections:

Jawetz, et al.: In the long-term management of 32 out patients: "Symptoms were controlled as bacteriuria was suppressed.... As infection was suppressed their renal function improved."[2]

Lippman, et al.: 49 patients treated from 1 month to 3 years: "In all of the patients treated successfully, the urine has remained completely clear"[3] as long as the drug was given.

Marshall and Johnson: 100 children treated for periods up to 27 months: FURADANTIN controlled "most infections initially and other infections by administration for a longer period. Prophylactically it was successful in suppressing recurrent infections."[4]

In the long-term control of chronic urinary tract infections, FURADANTIN "has characteristics that make it a valuable drug.... These include its lack of toxicity, wide range of antibacterial effectiveness and reduced tendency to induce development of bacterial resistance to the drug."[4]

Available as Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

References: 1. Lipscomb, H., et al.: South. M. J. 52:16, 1959. 2. Jawetz, E., et al.: A.M.A. Arch. Int. M. 100:549, 1957. 3. Lippman, R. W., et al.: J. Urol., Balt. 80:77, 1958. 4. Marshall, M., Jr., and Johnson, S. H., III: J. Am. M. Ass. 169:919, 1959.

NITROFURANS—a *unique* class of antimicrobials—
neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

NOW

. . . a new way to relieve pain and stiffness in muscles and joints

INDICATED IN:

- MUSCLE STIFFNESS
- LUMBOSACRAL STRAIN
- SACROILIAC STRAIN
- WHIPLASH INJURY
- BURSITIS
- SPRAINS
- TENOSYNOVITIS
- FIBROSITIS
- FIBROMYOSITIS
- LOW BACK PAIN
- DISC SYNDROME
- SPRAINED BACK
- "TIGHT NECK"
- TRAUMATIC STRAINS AND BRUISES
- POSTOPERATIVE MYALGIA



■ Exhibits unusual analgesic properties, different from those of any other drug ■ Specific and superior in relief of SOMAtic pain

■ Modifies central perception of pain without abolishing natural defense reflexes ■ Relaxes abnormal tension of skeletal muscle

SOMA™

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

■ More specific than salicylates ■ Less drastic than steroids

■ More effective than muscle relaxants

SOMA has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. SOMA is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with SOMA than with any previously used analgesic, sedative or relaxant drug.
SOMA also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

ACTS FAST. Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

NOTABLY SAFE. Toxicity of SOMA is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy on high dosage.

EASY TO USE. Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

SUPPLIED: Bottles of 50 white sugar-coated 350 mg. tablets.

Literature and samples on request.

WALLACE LABORATORIES, NEW BRUNSWICK, N. J.



The tyranny of the clock

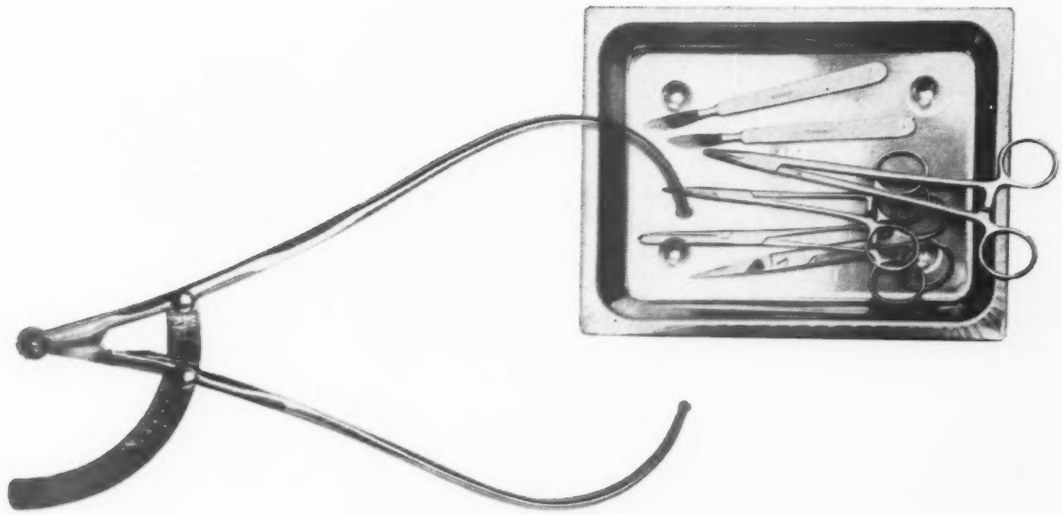
For many diabetics, time is a tyrant. No matter how inconvenient it may be, they must take their meals and injections "by the clock," or risk extremely disquieting reactions.

Orinase® makes it possible for you to lift this burden from most of these insulin-dependent patients. Given in conjunction with insulin, it smooths out the "peaks and valleys" of erratic blood sugar levels . . . "stabilizes" a surprising percentage of brittle diabetics.

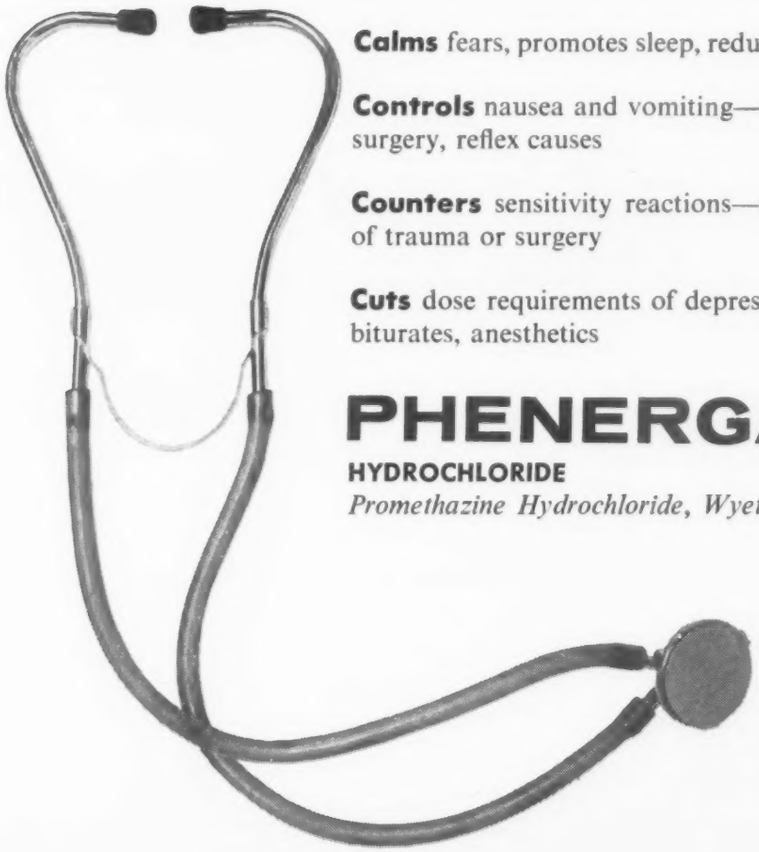
At the same time, it may enable you to reduce the insulin dosage for many insulin-dependent diabetics. ®TRADEMARK, REG. U. S. PAT. OFF. — TOLBUTAMIDE, UPJOHN

THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN

Upjohn **ORINASE**



In
MEDICINE
SURGERY
OBSTETRICS



Calms fears, promotes sleep, reduces postoperative excitement

Controls nausea and vomiting—motion sickness, pregnancy, surgery, reflex causes

Counters sensitivity reactions—allergy, drugs, tissue edema of trauma or surgery

Cuts dose requirements of depressant agents—narcotics, barbiturates, anesthetics

PHENERGAN®
HYDROCHLORIDE
Promethazine Hydrochloride, Wyeth

TABLETS
SYRUP
SUPPOSITORIES
INJECTION

Wyeth
Philadelphia 1, Pa.



in respiratory infections...

the new alternative

MADRIBON

"Structurally a sulfonamide but clinically in a class by itself, Madribon exerts a high degree of effectiveness against a wide range of pathogens...."

G. A. Moore, paper read at Conference on Recent Contributions to Antibacterial Therapy, New York City, May 21-22, 1959.

"The relatively minor change in the normal fecal flora... indicates considerably less likelihood of superinfections ...than with many other chemotherapeutic agents."

S. M. Finegold, Z. Kudinoff and H. O. Kendall, *ibid.*

"As Madribon does not materially alter the bacterial population of the respiratory tract, there is no danger of overgrowth as with antibiotics."

P. Rentchnick, paper presented at the International Congress of Infectious Pathology, Milan, Italy, May 6-10, 1959.

ROCHE LABORATORIES

In 25 years, antibacterials have progressed from the status of heroic therapy to universal medication. This development has brought into focus a number of unexpected problems relating both to bacterial and host response.

Shifts in bacterial flora—particularly of the respiratory, urinary and gastrointestinal tracts—pose entirely new therapeutic problems. The emergence of resistant strains of bacteria creates still another hazard. In addition, anaphylactic reactions often hamper critically needed therapy.

While this entire question of bacterial mutations and patient sensitization is undergoing continual intensive study and reorientation, the immediate clinical need is for a new alternative to control infection in today's patient.

A MODERN PROGRAM FOR THE CONTROL OF INFECTIONS

1.	In nonbacterial (presumably viral) upper respiratory infections	fluids, bed rest, antipyretics
2.	When the diagnosis is primary bacterial infection • when secondary bacterial invasion is a problem in virus infection • when sensitivity testing is not feasible	MADRIBON
3.	For problematic and fulminating infections	antibiotics

Backed by the fastest growing bibliography of any anti-infective agent, Madribon is already widely established as the new alternative because (1) it *quickly controls the infection* —in more than 90% of reported cases including some due to resistant strains; (2) it is *safe* —less than 2% side effects, generally of a mild nature; (3) it is *economical.*

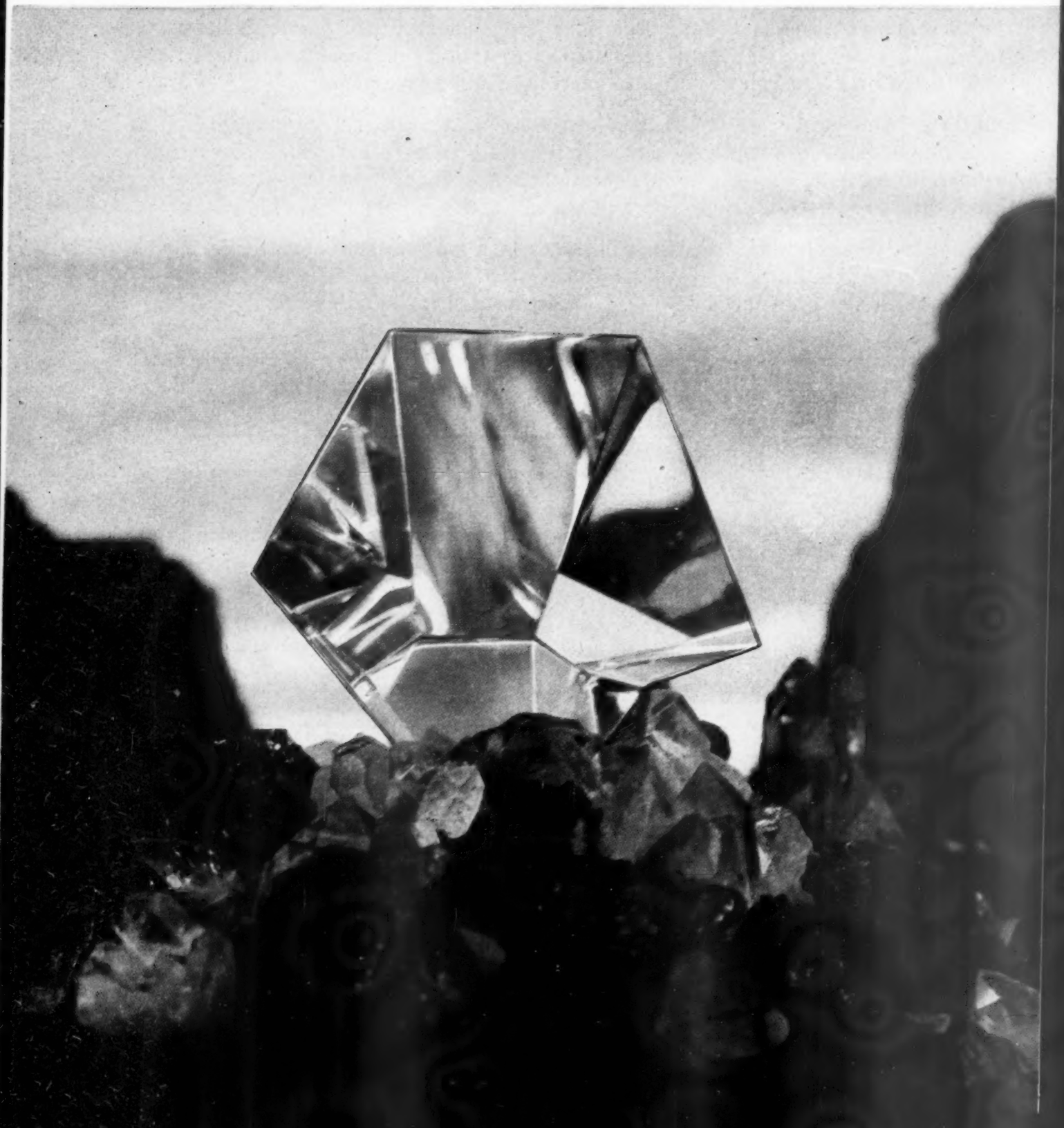
For recommended dosage and precautions, consult product literature.

Supplied: MADRIBON TABLETS: 0.5 Gm, double scored, monogrammed, gold colored—bottles of 30, 250 and 1000. MADRIQID CAPSULES: 125 mg, gold colored—bottles of 100 and 1000. MADRIBON SUSPENSION: 0.25 Gm/teasp. (5 cc), custard flavored—bottles of 4 oz and 16 oz.

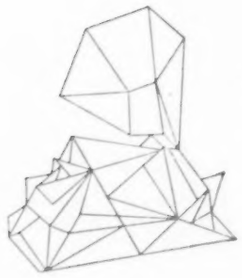
MADRIBON®—2,4-dimethoxy-6-sulfanilamido-1,3-diazine MADRIQID™ ROCHE®

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PURE ANTIHISTAMINE ACTION NOW A PHARMACOLOGIC FACT BECAUSE DĪSOMER SHEDS THE MOLECULAR DROSS



NEW...IN THE TREATMENT OF ALLERGIC DISORDERS



- *"...high therapeutic index"*[1]
- *unsurpassed clinical efficacy*
- *highly effective in exceptionally small doses*
- *side effects reduced to placebo level*

Disomer....a major scientific advance in the pharmacology of antihistamines!

DISOMER was described as being *"...as close to a pharmacologically pure form of histamine antagonist as the chemist can produce."*[1] Incorporating the newest knowledge of structure-function relationships, DISOMER comes closest thus far to the therapeutic ideal of pure antihistamine activity. DISOMER represents the *d*-isomer of racemic brompheniramine maleate. In shedding the *l*-isomer a high point in clinical effectiveness is achieved while side effects are reduced to the placebo level.

Therapeutic results have been noteworthy with 94.7% effectiveness reported.[2] Equally noteworthy is the virtual absence of clinically significant adverse reactions. Indeed, the sole side effect reported was occasional, mild drowsiness in only 4.7% of patients.

With DISOMER your allergic patient remains your alert patient while enjoying unsurpassed freedom from allergic symptoms. Ready now for your prescription—DISOMER is available in a variety of dosage forms to fit your patients' individual requirements.

Availability:

DISOMER CHRONOTAB*	6 mg.
DISOMER CHRONOTAB*	4 mg.
DISOMER Tablets	2 mg.
DISOMER Syrup	2 mg. per 5 cc.

Usual dosage:

6 mg. CHRONOTAB	b.i.d.
4 mg. CHRONOTAB	t.i.d.
2 mg. Tablet	q.i.d.
Syrup 1 teaspoonful	q.i.d.

**Chronotab* *is White's repeat-action tablet.*

References: (1) Gould, A. H. and Long, D. L.: Clinical Pharmacology and Therapeutic Use of Dexbrompheniramine Maleate (Disomer), a new Histamine Antagonist (submitted for publication). (2) Medical Department, White Laboratories, Inc.

WHITE LABORATORIES, INC.
Kenilworth, New Jersey

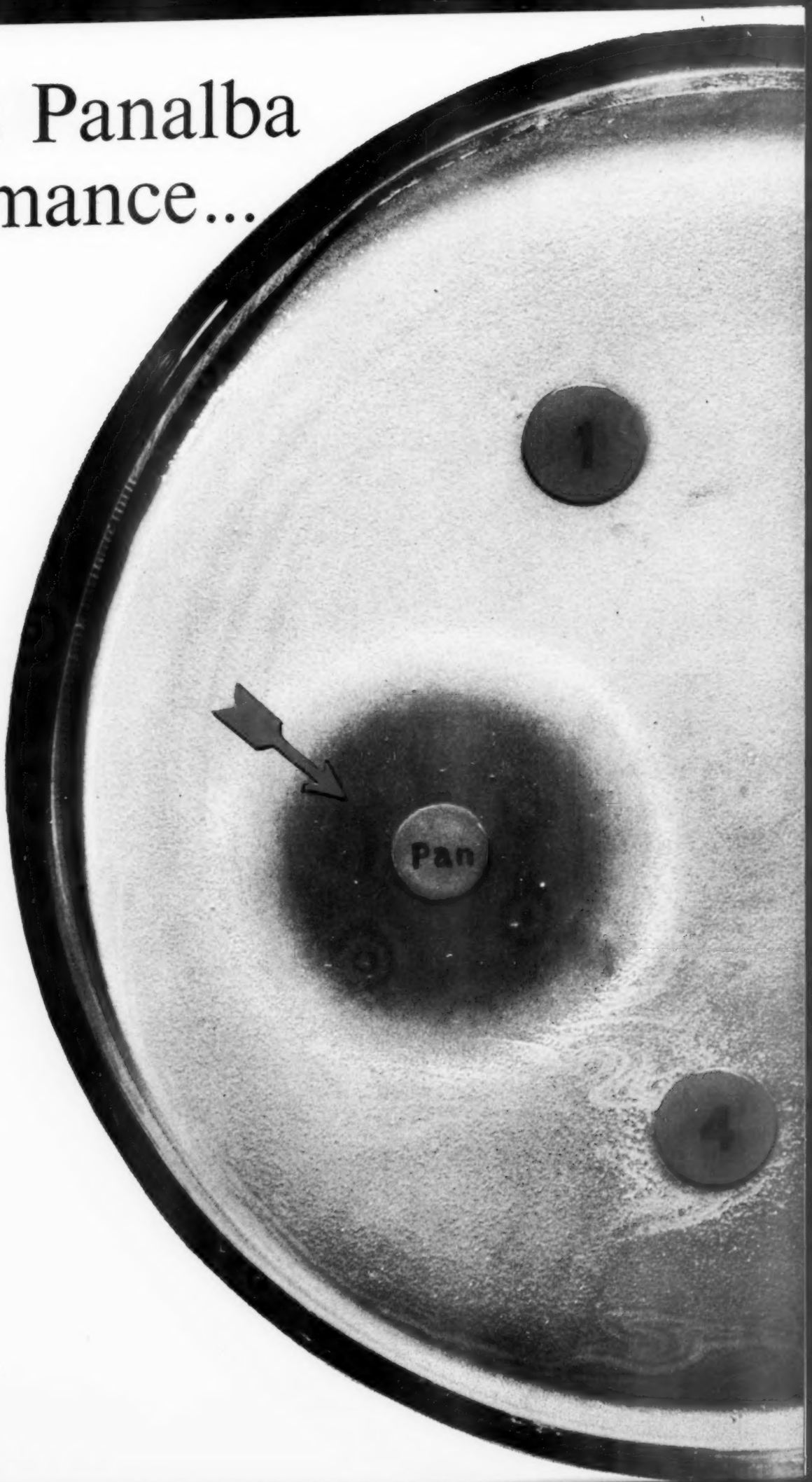
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DEXBROMPHENIRAMINE MALEATE

...sheds the molecular dross

This is Panalba performance...





in pneumonia

. . . into a mixed culture of the three organisms commonly involved in pneumonia . . . *K. pneumoniae*, *Diplococcus pneumoniae*, and *Staphylococcus aureus* (in this case a resistant strain) . . . we introduce the five most frequently used antibiotics.

Twenty-four hours later (in this greatly enlarged photograph), note that only *one* of the five leading antibiotics has stopped *all* the organisms, including the resistant staph! This is Panalba.

In your next pneumonia patient . . . in *all* your patients with potentially-serious infections . . . provide this extra protection with your prescription :

Dosage—1 or 2 capsules 3 or 4 times a day.
Supplied—Capsules containing Panmycin phosphate equivalent to 250 mg. tetracycline hydrochloride, and 125 mg. Albamycin as novobiocin sodium, in bottles of 16 and 100.
Now available: **new Panalba Half-Strength Capsules in bottles of 16 and 100.**

Panalba*

(Panmycin* Phosphate plus Albamycin*)

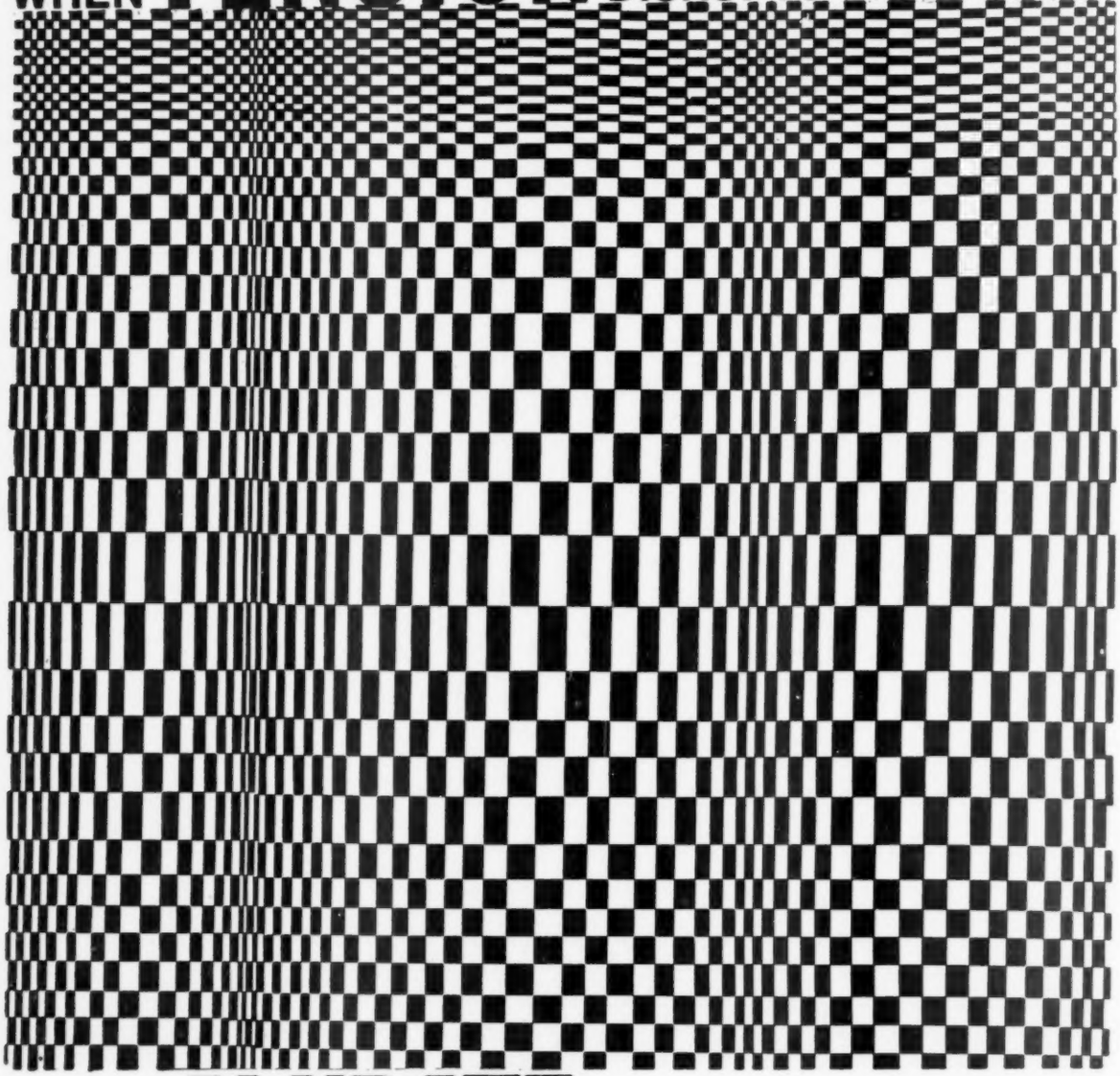
The broad-spectrum antibiotic of *first* resort



Upjohn The Upjohn Company Kalamazoo, Michigan

*TRADEMARK, REG. U. S. PAT. OFF.

WHEN TENSION DISRUPTS TREATMENT



ELIXIR ALURATE DISRUPTS TENSION

Dependable, prompt-acting daytime sedative.

Broad margin of safety. Virtually no drowsiness. Over a quarter century of successful clinical use. Alurate is effective by itself and compatible with a wide range of other drugs. To avoid barbiturate identification or abuse, Alurate is available as Elixir Alurate (cherry-red) and Elixir Alurate Verdum (emerald-green).

Adults: ½ to 1 teaspoonful of either Elixir Alurate or Elixir Alurate Verdum, 3 times daily. ALURATE®—brand of aprobarbital.

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breakfast on the run... lunch on the job... time for Myadec®

high potency vitamin-mineral formula

When dietary habits are poor, MYADEC helps prevent vitamin-mineral deficiencies by providing comprehensive nutritional supplementation. Just one capsule daily supplies therapeutic doses of nine important vitamins plus significant quantities of eleven essential minerals and trace elements.

Each MYADEC Capsule contains:

VITAMINS:

Vitamin B_{12} crystalline	5 mcg.
Vitamin B_2 (riboflavin)	10 mg.
Vitamin B_6 (pyridoxine hydrochloride)	2 mg.
Vitamin B_1 mononitrate	10 mg.
Nicotinamide (niacinamide)	100 mg.
Vitamin C (ascorbic acid)	150 mg.
Vitamin A	(7.5 mg.) 25,000 units
Vitamin D	(25 mcg.) 1,000 units
Vitamin E (d-alpha-tocopheryl-acetate concentrate)	5 I.U.

MINERALS (as inorganic salts):

Iodine	0.15 mg.
Manganese	1.0 mg.
Cobalt	0.1 mg.
Potassium	5.0 mg.
Molybdenum	0.2 mg.
Iron	15.0 mg.
Copper	1.0 mg.
Zinc	1.5 mg.
Magnesium	6.0 mg.
Calcium	105.0 mg.
Phosphorus	80.0 mg.

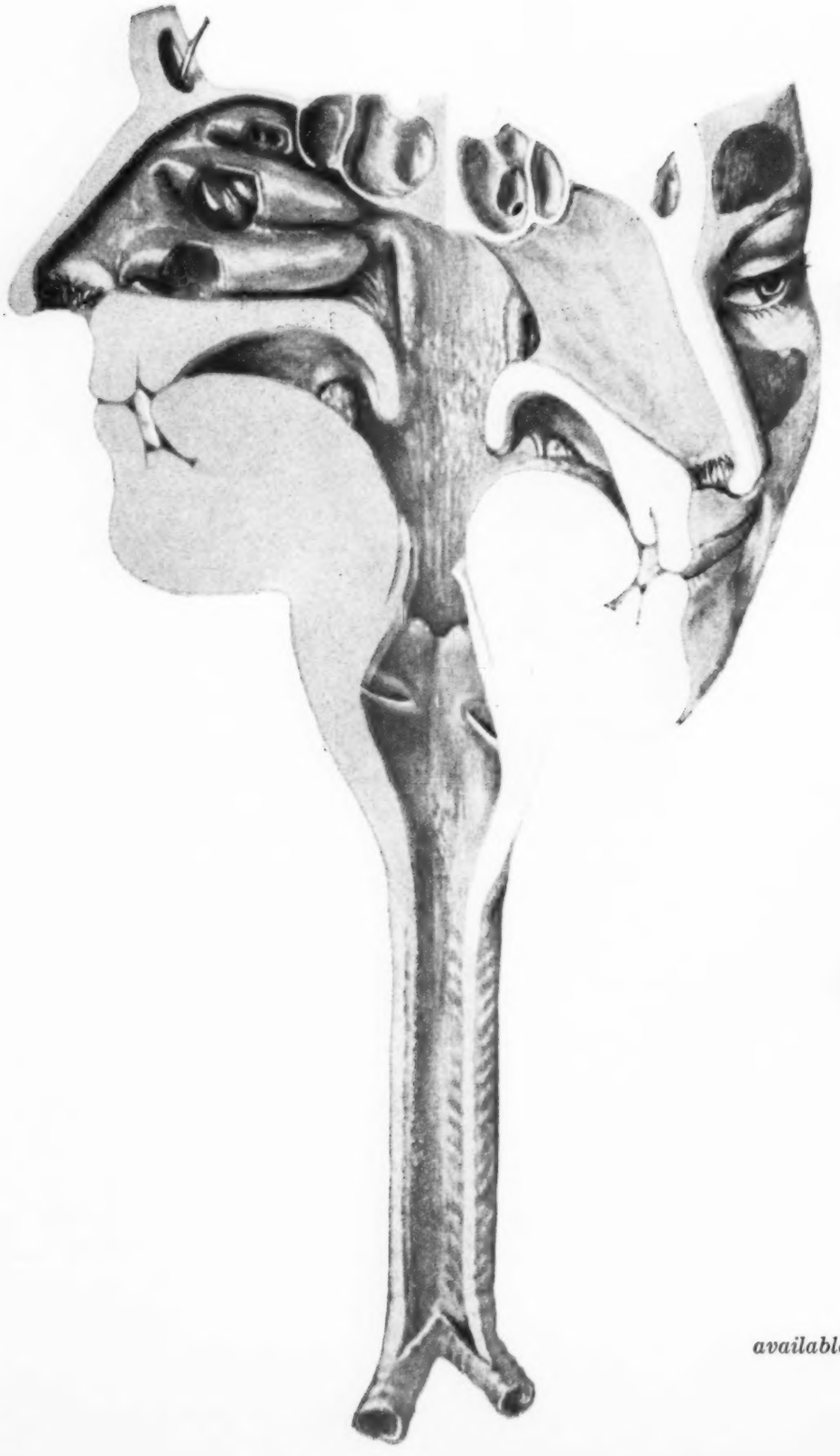
Bottles of 30, 100, 250, and 1,000.

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ALL QUIET ON THE



LATEST ADVANCE IN SINUS AND NASAL DECONGESTION

SPECIFIC COUGH MODERATOR

BROAD RANGE COUGH/COLD FORMULATION

available only on your prescription

COUGH/COLD FRONT

"KRYL" TABLETS
for prompt, sustained decongestant effect

ANTIHISTAMINE ACTION WITHOUT SEDATION
SYSTEMIC DECONGESTION WITHOUT SIDE EFFECTS
ANALGESIC-ANTIPYRETIC ACTION WITHOUT DRUG STIMULATION
ANTI-STRESS VITAMIN TO MAINTAIN TISSUE INTEGRITY

Each tablet contains:

Isothipendyl HCl ("Theruhistin®") ...	4 mg.
Aspirin	230 mg.
Phenacetin	160 mg.
l-Phenylephrine HCl ..	5 mg.
Ascorbic Acid*	100 mg.

USUAL DOSAGE: Adults, 2 tablets initially, then 1 tablet every four hours. Children (6 to 12), half the adult dose.

SUPPLIED: No. 746 — bottles of 100 and 1,000 tablets.

"COTHERA"® SYRUP
for control of useless/harmful cough

Brand of Dimethoxanate hydrochloride

Acts Selectively — to subdue but not abolish the cough reflex. **Safely** — non-narcotic. non-constipating. no toxicity reported. **Swiftly** — acts within minutes... lasts for hours, often providing nightlong relief with a single dose. **Surely** — preferred to dihydrocodeinone by 4 out of 5 patients.*

*Klein, B.: Antibiotic Med. 5:462 (July) 1958.

"COTHERA"® COMPOUND
for relief *beyond* cough control

MODERATES THE COUGH PROMPTLY—SPECIFICALLY
without sedation and respiratory depression
COUNTERACTS HISTAMINE-INDUCED SYMPTOMS
with full potency and virtually no sedation
RELIEVES SINUS AND NASAL BLOCKAGE
by direct, sustained vasoconstricting effect
RELIEVES PAIN, FEVER, AND HEADACHE
through potent but selective central action
SOOTHES IRRITATED MUCOSA AND PROMOTES EXPECTORATION
by demulcent, liquefying, and counterirritant properties

IN PALATABLE SYRUP FORM
Each 5 cc. (one teaspoonful) contains:

Dimethoxanate HCl ...	25 mg.
Isothipendyl HCl ("Theruhistin®") ...	2 mg.
l-Phenylephrine HCl ..	5 mg.
Acetaminophen	100 mg.
Ammonium chloride ...	100 mg.
Sodium citrate	50 mg.
Chloroform	0.25%

Contains 10% alcohol

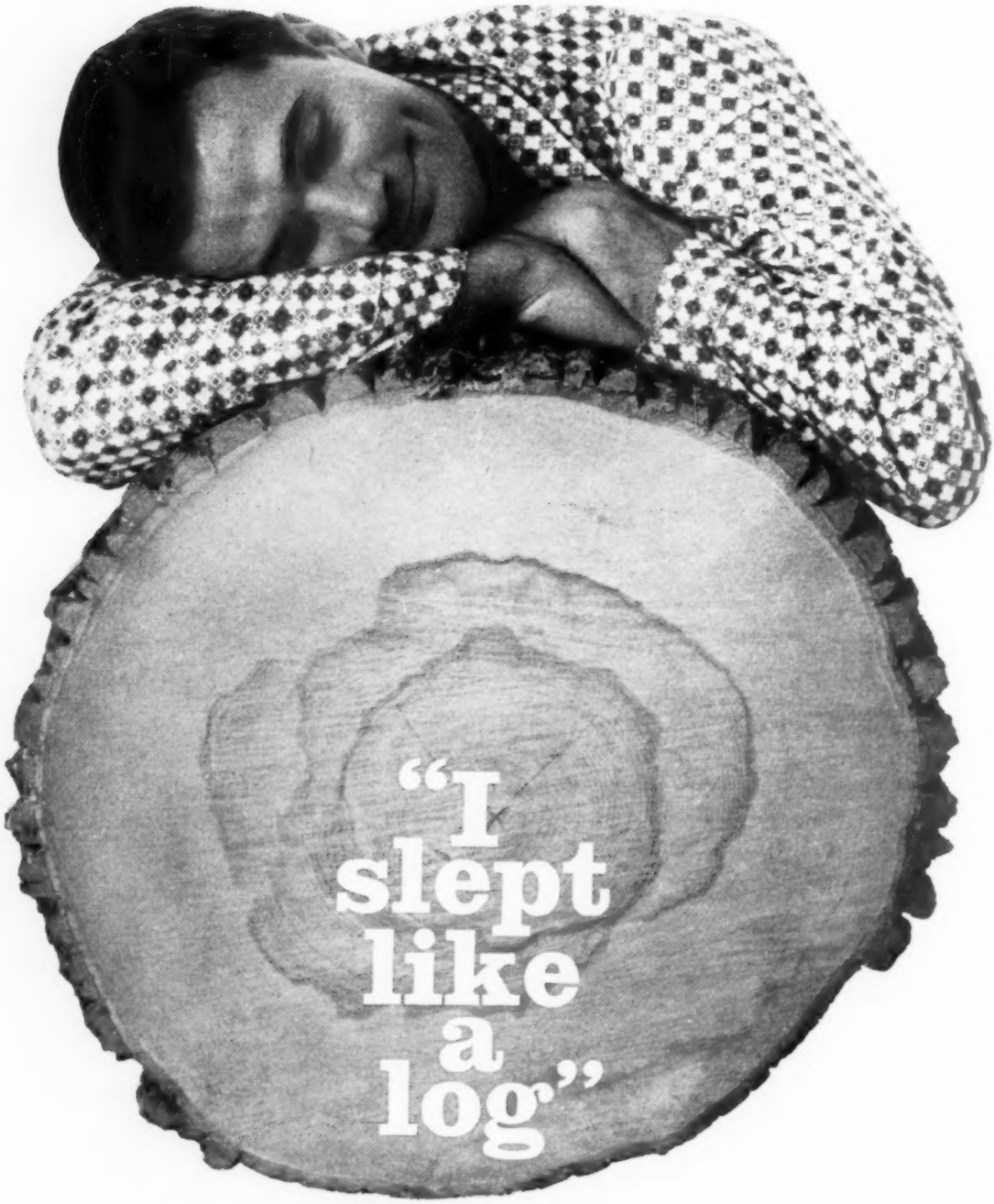
USUAL DOSAGE: For both "Cothera" Syrup and "Cothera" Compound—Adults and children over 8 years—1 to 2 teaspoonfuls (5 to 10 cc.). Children (2 to 8 years)—1/2 to 1 teaspoonful. Three or four times daily.

SUPPLIED: "Cothera" Syrup, No. 934 — Dimethoxanate hydrochloride, 25 mg. per 5 cc. (tsp.); "Cothera" Compound, No. 936 — Bottles of 16 fluidounces and 1 gallon.

Ayerst®

AYERST LABORATORIES New York 16, N.Y. • Montreal, Canada

5949



new Noludar 300

300 mg CAPSULES

A good night's sleep can be described in many ways, but "natural" comes closest to the kind of sound, refreshing sleep your patients will enjoy when you prescribe new **NOLUDAR 300.** Prompt action... unsurpassed safety... 6 to 8 hours of undisturbed rest...and a cheerful awakening without barbiturate "hangover"—such is the quality of sleep with **NOLUDAR.**

NOLUDAR®—brand of methyprylon

Safe, non-barbiturate, non-addictive, eminently free of even minor side reactions.

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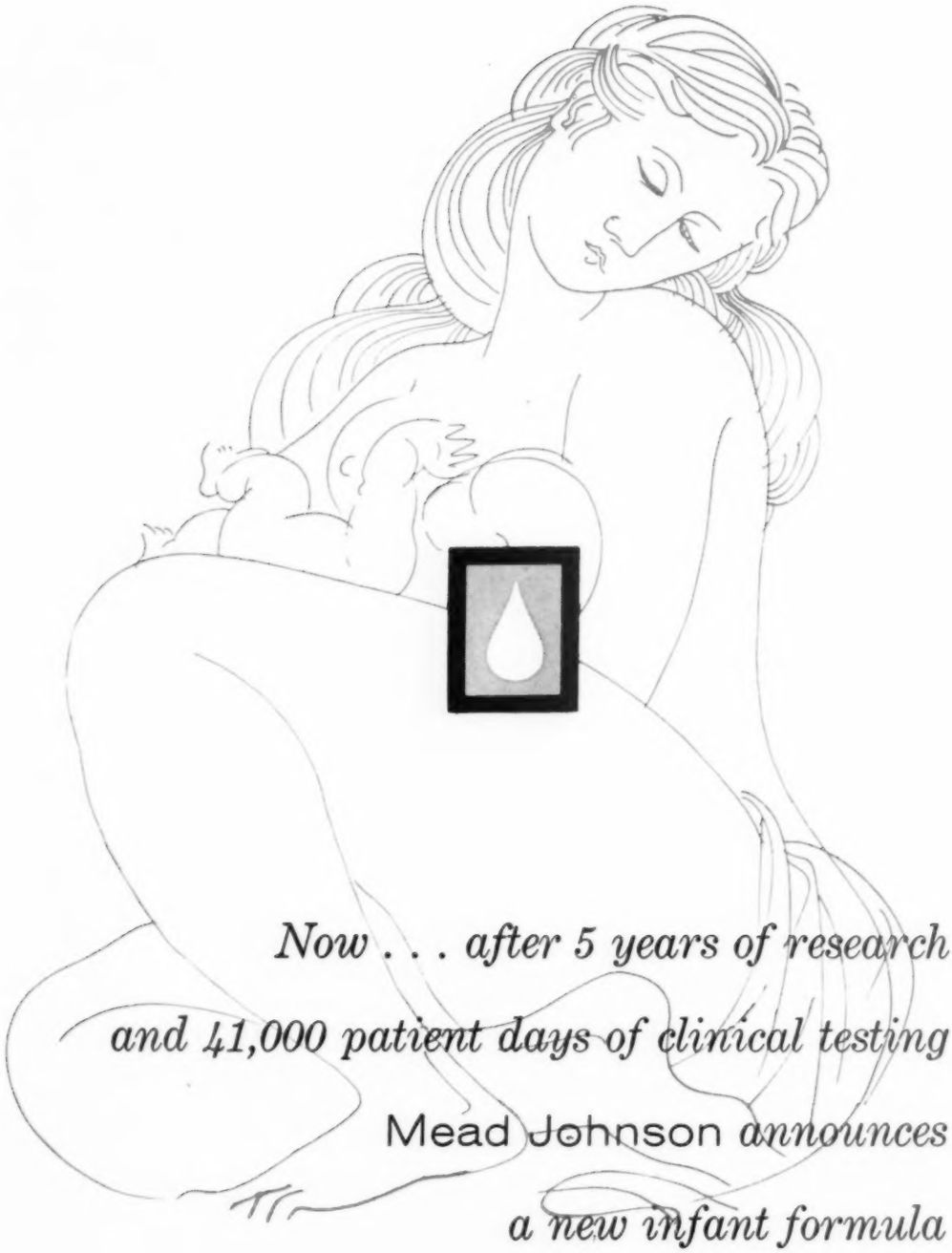
new Noludar 300

300 mg CAPSULES

Now a Noludar dosage form for every sedative-hypnotic need

When sleeplessness is a real problem	For gentle hypnotic effect	For daytime sedation
NOLUDAR 300 mg	**NOLUDAR 200** mg	**NOLUDAR 50** mg
1 capsule at bedtime	1 tablet at bedtime	50 to 100 mg three or four times daily

ROCHE LABORATORIES • Division of Hoffmann-La Roche Inc • Nutley 10, New Jersey



Now . . . after 5 years of research

and 41,000 patient days of clinical testing

Mead Johnson *announces*

a new infant formula

---

nearest to mother's milk[1]

in nutritional breadth and balance

Enfamil*

Infant formula

nearest to mother's milk[1]

in nutritional breadth and balance

In a well controlled institutional study[2], using the Latin Square technic† for the first time in infant nutritional research, Enfamil was compared with three widely used infant formula products.

This formula produced:

weight gains greater than average
stool firmness between firm and soft . . . and
lower stool frequency.

NEAREST . . . to mother's milk in its pattern of protein, fat and carbohydrate by caloric distribution

NEAREST . . . to mother's milk in its pattern of vitamins and minerals (except for more vitamin D in accordance with NRC recommendations)

NEAREST . . . to mother's milk in its fat composition (no butterfat; no sour regurgitation)

NEAREST . . . to mother's milk in its ratio of saturated to unsaturated fatty acids

NEAREST . . . to mother's milk in its low renal solute load

ENFAMIL LIQUID—cans of 13 fluid ounces.
1 part Enfamil Liquid to 1 part water for 20 cal. per fl. oz.

ENFAMIL POWDER—cans of 1 lb., with measure.
1 packed level measure of Enfamil Powder to 2 ounces of water for 20 cal. per fl. oz.

†The Latin Square technic, used for the first time in infant nutritional research to evaluate Enfamil, is a change-over method for intensive, controlled clinical testing which was applied to infants during their critical first 8 weeks of life. It is an efficient way of neutralizing the multiple variables in nutritional research.

1. Macy, I. G.; Kelly, H. J., and Sloan, R. E., with the Consultation of the Committee on Maternal and Child Feeding of the Food and Nutrition Board, National Research Council: The Composition of Milks. National Academy of Sciences, National Research Council, Publication 254, Revised 1953. 2. Research Laboratories, Mead Johnson & Company.

Mead Johnson
Symbol of service in medicine

*Trade Mark

how often have you thought...

"...but how will it work in my practice?"

This most frequently asked question cannot be answered by the manufacturer, the detail man, an advertisement, a piece of mail. Only through actual experience with a product in day-to-day private practice can this question be answered.

UNITENSEN PROVED IN DAY-TO-DAY PRACTICE In office trials, Unitensen products have been proved effective therapy in the management of the hypertensive patient. These are the facts, obtained from 3,841 physicians, who used Unitensen products in their day-to-day office practice, in treating a total of 35,727 patients. In 11,093 cases (31.0%) results were "excellent"; in 51.2% (18,294) cases, "good"; "fair" results were obtained in 4,591 patients (12.9%) and in only 1,749 cases (4.9%) were results "unsatisfactory." Minor side effects were reported in 1,081 cases (3.0%).

The results mentioned above were obtained while the patients engaged in their normal daily occupations and activities. None of the patients involved in the study were hospitalized or institutionalized. And, despite such variables as dietary indiscretions, an occasional overdose, or a dose inadvertently "missed," the Proof In Practice Study shows Unitensen products to be safe, dependable, potent antihypertensive therapy . . . permitting practical office management of virtually all hypertensive cases.

UNITENSEN: BASIC HYPERTENSIVE THERAPY Although many of the patients in the Study also received diuretics and/or tranquilizers during the course of treatment, it was noted that the vasodilating effect of Unitensen was required to obtain optimum blood pressure control. Unitensen, a true hypotensive agent, is potentiated by diuretics. A combination of the two is frequently recommended for lower dosage of each drug, minimizing the side effects of either.

UNITENSEN DOES MORE THAN LOWER BLOOD PRESSURE Dr. Burton M. Cohen* makes the following observations regarding Unitensen:

"Hypotensive effect obtained through specific stimulation of afferent side of reflex pathways of blood pressure control without adrenolytic action or ganglionic blocking . . . Nausea and vomiting rare . . . No alteration of vasomotor reflexes, thus no postural collapse . . . Bradycardia, never tachycardia, may occur . . . Cardiac output not lessened . . . Renal circulation participates in reflex vasodilation . . . Cerebrovascular resistance is decreased, with improvement or maintenance of blood flow and O_2 utilization . . . No dangerous side actions have been reported."*

UNITENSEN-R® Each tablet contains cryptenamine (tannates) 1.0 mg., reserpine, 0.1 mg.

UNITENSEN-PHEN® Each tablet contains cryptenamine (tannates) 1.0 mg., phenobarbital, 15 mg.

UNITENSEN® Each tablet contains cryptenamine (tannates) 2.0 mg.

Clinical supplies available on request.

Neisler IRWIN, NEISLER & CO. • Decatur, Illinois

*Cohen, B. M.: The Ambulatory Patient with Hypertension: An Approach to Office Management, presented at the American Medical Association Convention, San Francisco, California, June 22-27, 1958.

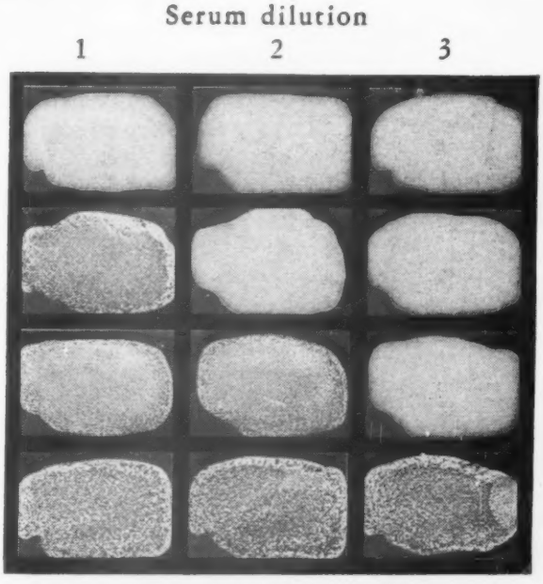
NEW

rapid screening test for AGAMMA-globulinemia

and other abnormal levels of serum gamma globulin

Hyland GG-TEST*

an accurate test for estimating the 4 clinically significant levels of serum gamma globulin



*Trade Mark of Hyland Laboratories

Hyland GG-TEST requires only one drop of patient's serum and is performed simply and quickly on a glass slide (reactions in less than 2 minutes). Permits routine GG serum level determinations at low cost without overtaxing laboratory facilities.

Supplied: Kit containing Latex-Anti-Human Gamma Globulin Reagent and Glycine-Saline Buffer Diluent for 40 tests, Normal Serum Controls diluted ready for use, capillary pipettes for preparing serum dilutions, divided glass slide, and complete directions for the test. $15.00 per kit.

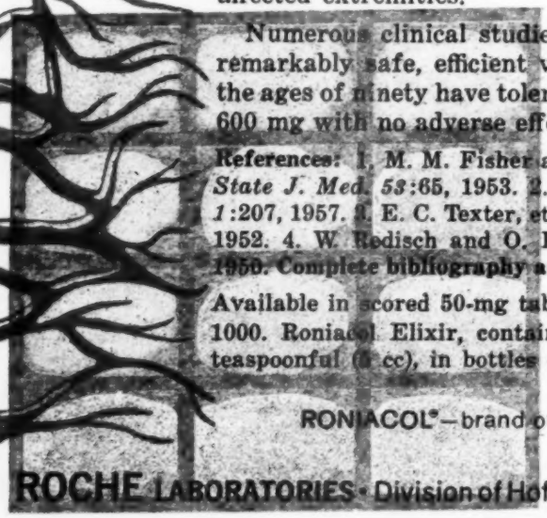
Hyland laboratories

Hyland

4501 Colorado Blvd., Los Angeles 39, California • 160 Lockwood Ave., Yonkers, New York

There are NO KNOWN CONTRA-INDICATIONS

Peripheral vasospasm of any etiology may be effectively treated with Roniacol without fear of complications. Roniacol is metabolized to the pure vitamin form (nicotinic acid)...acts by a direct relaxing effect on peripheral blood vessels to increase and intensify blood flow to affected extremities.



Numerous clinical studies[1-4] show Roniacol to be a remarkably safe, efficient vasodilator. "Patients up to the ages of ninety have tolerated the drug in doses up to 600 mg with no adverse effects."[1]

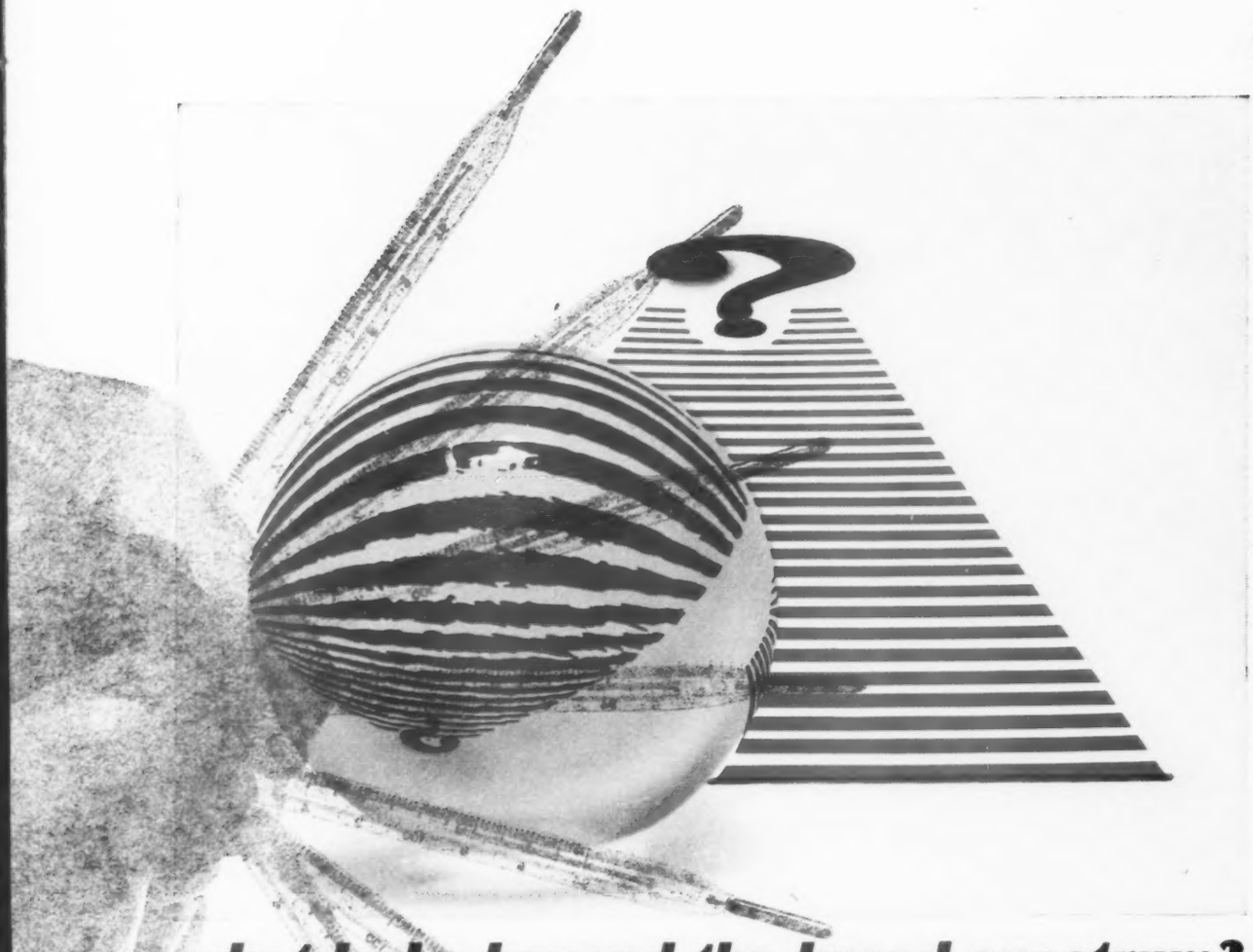
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Available in scored 50-mg tablets, bottles of 100, 500, and 1000. Roniacol Elixir, containing 50 mg of Roniacol per teaspoonful (5 cc), in bottles of 16 ounces and one gallon.

RONIACOL®—brand of beta-pyridyl carbinol

ROCHE LABORATORIES · Division of Hoffmann-La Roche Inc · Nutley 10, New Jersey

RONIACOL for vasodilation



what lurks beyond the broad spectrum?

"Broad spectrum" has evolved into an especially apt term to describe a growing number of "specialized" antibiotics. These provide the best means of destroying pathogenic bacteria which range all the way from large protozoa through gram-negative and gram-positive bacteria to certain viruses at the far end of the spectrum.

But beyond the spectrum lurk pathogenic fungi. Aggressive infections often require intensive broad spectrum antibiotic attack. It becomes more apparent every day that fungal superinfections may occur during or following a course of such therapy.[1,2] Long term debilitating disease, diabetes, pregnancy, corticosteroid therapy, and other causes may predispose to such fungal infections[1,3,4] as iatrogenic moniliasis. These facts complicate the administration of antibiotics.

Mysteclin-V controls both – infection and superinfection. Mysteclin-V makes a telling assault on bacterial infections and, in addition, prevents the potentially dangerous monilial overgrowth.[2,5-8] Mystèclin-V is a combination of the phosphate complex of tetracycline – for reliable control of most infections encountered in daily practice – and Mycostatin, the first safe antifungal antibiotic.

Case history after case history marked "recovered" provides clinical evidence of the special merit of this advance in specially designed antibiotics. When you prescribe Mysteclin-V, you provide "broad therapy" with extra protection that extends beyond the spectrum of ordinary antibiotics.

'MYSTECLIN'®, 'SUMYCIN'®, AND 'MYCOSTATIN'® ARE SQUIBB TRADEMARKS

Supplied:

	Tetracycline Phosphate Complex equiv. Tetracycline HCl (mg.)	Mycostatin units
Mysteclin-V Capsules (per capsule)	250	250,000
Mysteclin-V Half-Strength Capsules (per capsule)	125	125,000
Mysteclin-V Suspension (per cc.)	25	25,000
Mysteclin-V Pediatric Drops (per cc. – 20 drops)	100	100,000

References: 1. Dowling, H. F.: Postgrad. Med. 23:554 (May) 1958. 2. Finland, M.: Antibiotics Annual 1955-1956, New York, Medical Encyclopedia Inc., 1956, p. 776. 3. Lund, H.: In Elek, S. D.: Ed. Antibiotics Ann. 1956-1957, New York, Med. Encyclopedia, Inc., 1957, p. 1. 4. Rein, C. R.; Lewis, L. A., and Dick, J. D.: Antibiotic Med. & Clin. Ther. 4:771 (Dec.) 1957. 5. Welch, H.: Antibiotics Annual 1955-1956, New York, Medical Encyclopedia Inc., 1956, p. 862. 6. Campbell, E. A.; Prigot, A., and Dorsey, G. M.: Antibiotic Med. & Clin. Ther. 4:941 (Dec.) 1957. 7. Chamberlain, J. G.; Corroon, H. E., and Hammond, J.: Antibiotic Med. & Clin. Ther. 5:521 (Aug.) 1958. 8. From, P., and Ali, J. H.: Antibiotic Med. & Clin. Ther. 5:639 (Nov.) 1958.

Mysteclin-V

SQUIBB TETRACYCLINE PHOSPHATE COMPLEX (SUMYCIN) AND NYSTATIN (MYCOSTATIN)

Squibb Quality
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in oral penicillin therapy

the speed of action you want

the reliability you need

Penicillin, still the most frequently prescribed antibiotic, assumes new reliability in the form of PEN•VEE K. Tablet or Liquid PEN•VEE K may be prescribed for all infections responsive to oral penicillin . . . *including many usually treated with parenteral penicillin.*

The speed of action and reliability of oral potassium penicillin V have been dramatically demonstrated by recent studies[1,2] in which 107 subjects were each given 400,000 units of the antibiotic. Appreciable penicillin levels were consistently produced within 15 minutes; peak levels within one-half hour. Penicillin levels still persisted in all subjects at two hours, and in 93 per cent of subjects at four hours.

1. Peck, F.B., Jr., and Griffith, R.S.: Antibiotics Annual 1957-1958, Medical Encyclopedia, Inc., p. 1004. 2. Wright, W.W., and Welch, H.: Antibiotic Med. *5*:139 (Feb.) 1958.

PEN·VEE® K

Liquid: Penicillin V Potassium for Oral Solution;
Tablets: Penicillin V Potassium, Wyeth

Wyeth®
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SUPPLIED: *Liquid*: raspberry-flavored, 125 mg. (200,000 units) per 5-cc. teaspoonful; peach-flavored, 250 mg. (400,000 units) per 5-cc. teaspoonful. Both supplied as vials of powder to make 40 cc. *Tablets*: 125 mg. (200,000 units) and 250 mg. (400,000 units) in vials of 36.

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you provide vitamin protection to help maintain health and energy during the early years of rapid growth.

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Each 0.6 cc. supplies:

Vitamin A	5,000 units
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Vitamin C (ascorbic acid)	50 mg.
Vitamin B_1 (thiamine hydrochloride)	1 mg.
Vitamin B_2 (riboflavin)	1.2 mg.
Vitamin B_6 (pyridoxine hydrochloride)	1 mg.
Pantothenic acid (as the sodium salt)	5 mg.
Nicotinamide (niacinamide)	10 mg.

In bottles of 15 and 50 cc. with calibrated plastic droppers.

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tablets · alka capsules — **potent · nonhormonal · anti-inflammatory agent**

BUTAZOLIDIN tablets or the Alka capsules are **equally effective but individually adaptable in a wide range of arthritic disorders.**

Recent clinical reports continue to justify the selection of Butazolidin for rapid relief of pain, increased mobility, and early resolution of inflammation.

Gouty Arthritis: "...95 per cent of patients experienced a satisfactory response..."[1]

Rheumatoid Arthritis: In "A total of 215 cases...over half, 50.7 per cent showed at least major improvement...with 21.8 per cent showing minor improvement..."[2] **Osteoarthritis:** 301 cases showed a total of 44.5 per cent with complete remission or major improvement. In the remainder, 28.2 per cent showed minor improvement.[2] **Spondylitis:** All patients "experienced initial major improvement that was maintained throughout the period of medication."[3] **Painful Shoulder Syndromes:** Response of 70 patients with various forms showed 38.6 per cent complete remissions, 37.1 per cent major improvement, 20.0 per cent minor improvement..."[2]

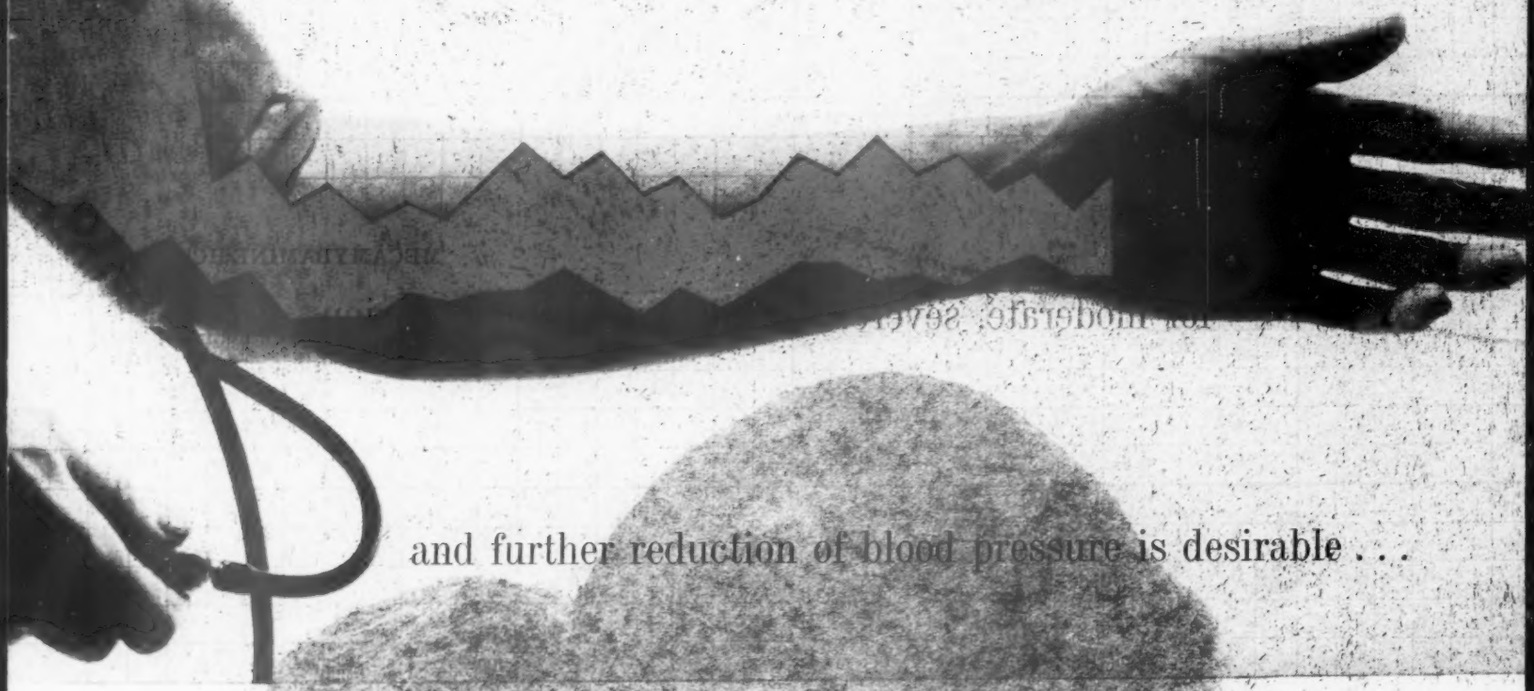
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Availability BUTAZOLIDIN® (phenylbutazone GEIGY): Red coated tablets of 100 mg. BUTAZOLIDIN® Alka: Capsules containing BUTAZOLIDIN® (phenylbutazone GEIGY), 100 mg.; dried aluminum hydroxide gel, 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide, 1.25 mg.

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when the response to other hypotensive agents is inadequate . . .



and further reduction of blood pressure is desirable . . .

adding ganglionic-blocking

INVERSINE®

MECAMYLAMINE HCl

often makes possible a lessening of cardiovascular-renal damage, regression of the basic disease, and prolongation of life

"unnecessary delay must be avoided in establishing ganglion blockade in severe or malignant hypertension"

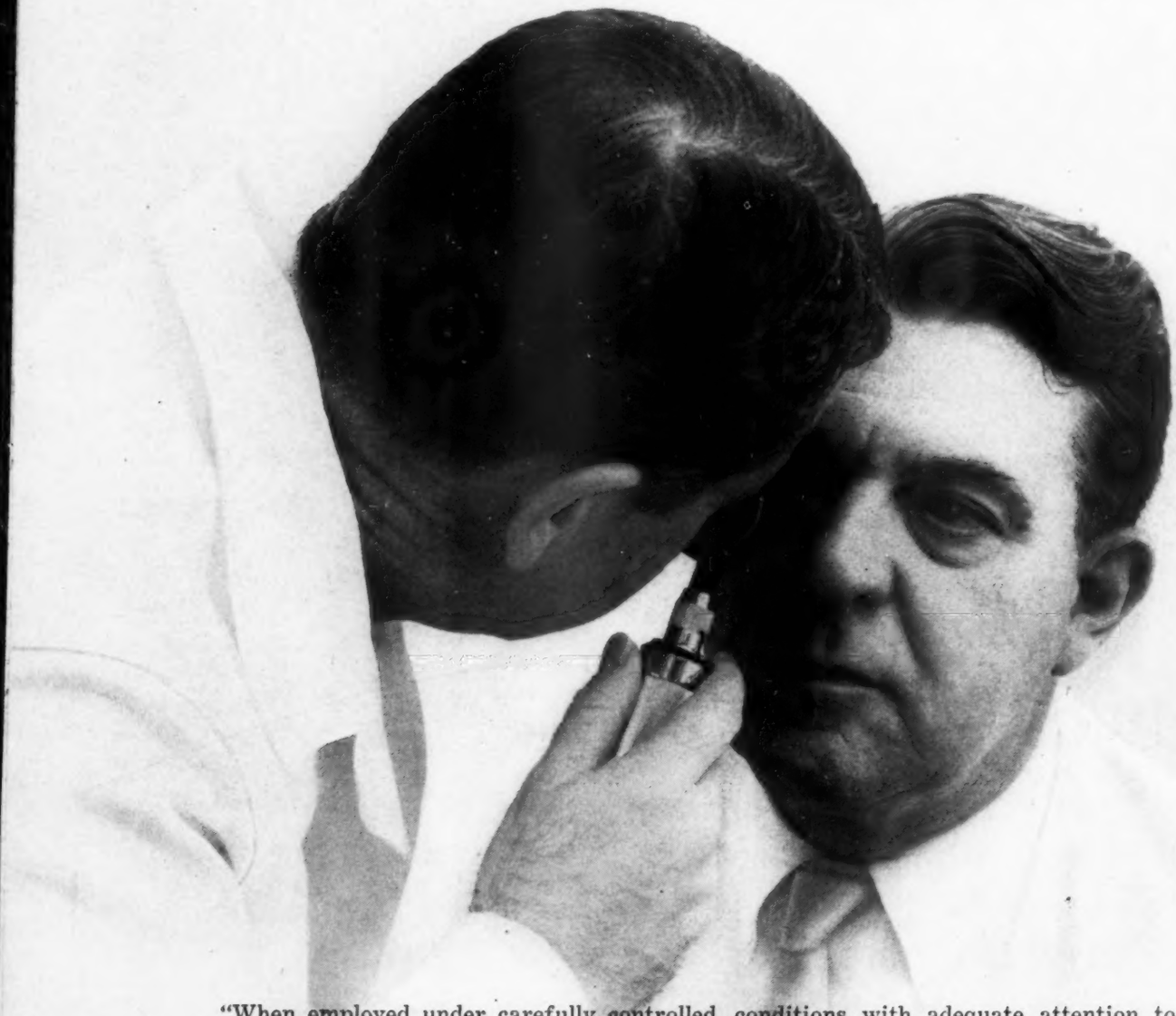
Beem, J. R., and Moyer, J. H.: Geriatrics 13:378, June 1958.

relieve high blood pressure and its manifestations

INVERSINE®

MECAMYLAMINE HCl

for moderate, severe, and malignant hypertension



"When employed under carefully controlled conditions with adequate attention to proper regulation of dosage, mecamylamine ['INVERSINE'] may be expected to reduce blood pressure effectively and to ameliorate various manifestations of hypertensive-cardiovascular disease. These include such symptoms as headache, dizziness, vertigo, hypertensive encephalopathy, cerebral or subarachnoid hemorrhage, retinopathy, cardiac hypertrophy and, in some cases, cardiac decompensation."

A.M.A. Council on Drugs, New and Nonofficial Drugs: Philadelphia, J. B. Lippincott Co., 1958, p. 285

A GREATLY IMPROVED GANGLIONIC BLOCKING AGENT

'INVERSINE'

- of the orally effective blocking agents, only 'INVERSINE' is completely and uniformly absorbed
- because it is uniformly absorbed, 'INVERSINE' provides predictable, reproducible effects with minimal day-to-day fluctuations
- has a gradual onset of effect, reducing the likelihood of sudden drops in blood pressure
- effective in extremely low dosage (orally, 10 mg. 'INVERSINE' is approximately equivalent to 100 mg. pentolinium, 80 mg. chlorisondamine, 1000 mg. hexamethonium)
- has a long duration of action (6 to 12 hours or longer), permitting convenient dosage schedules
- development of tolerance is not as pronounced as with other ganglionic blocking drugs
- effective in many patients who do not respond to other ganglionic blocking drugs

pretreatment with 'Diuril', or 'Diuril' and rauwolfia, enhances therapy with 'Inversine'

"Pretreatment with chlorothiazide ['DIURIL'] and rauwolfia reduces the dosage requirement, augments blood pressure response, and moderates certain of the side effects of ganglion blocking agents. Although such basal therapy is advantageous, unnecessary delay must be avoided in establishing ganglion blockade in severe or malignant hypertension."

Beem, J. R., and Moyer, J. H.: Geriatrics 13:378, June 1958

dosage recommendations for new patients

1. *Initiate therapy with 'DIURIL'*
'DIURIL' is given in a dosage range of from 250 mg. twice a day to 500 mg. three times a day, depending on severity of the hypertension.

2. *Add other agents*
Other drugs (rauwolfia, 'INVERSINE', hydralazine, etc.) are added as necessary and their dosage adjusted according to patient response.

'INVERSINE' is given in the same manner whether used with other drugs or alone. Recommended initial dosage is 2.5 mg. twice a day, preferably after meals. May be increased by 2.5 mg. at intervals of no less than two days until desired response is obtained. In severe or urgent cases, the increments may have to be larger or more frequent, with the largest dose given preferably at noon or in the evening. 'INVERSINE' is extremely potent and should always be titrated according to the patient's orthostatic blood pressure response.

3. *Adjust dosage of all medication*
The patient must be observed frequently and careful adjustment of all agents should be made to determine optimal maintenance dosage.

Precautions: Side effects of 'INVERSINE' are essentially the same as those encountered with other ganglionic blocking agents. At the first sign of constipation, vigorous treatment must be initiated immediately since paralytic ileus may result if constipation is unchecked. Patients should be informed how to cope with postural hypotension should this occur. 'INVERSINE' is contraindicated in coronary insufficiency, organic pyloric stenosis and recent myocardial infarction. Additional information on 'INVERSINE' and 'DIURIL' is available on request.

Supplied: 'INVERSINE', tablets of 2.5 and 10 mg. Bottles of 100.
'DIURIL', tablets of 250 mg. and 500 mg. Bottles of 100 and 1000.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

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PARAFON®

(PARAFLEX® + TYLENOL®)

for muscle relaxation plus analgesia

prescribe PARAFON in low back pain—sprains—strains—rheumatic pains

Each PARAFON tablet contains:

PARAFLEX® Chlorzoxazone† ..... 125 mg.
Specific for skeletal muscle spasm

TYLENOL® Acetaminophen ..... 300 mg.
The analgesic preferred in musculoskeletal pain

Dosage: Two tablets t.i.d. or q.i.d.

Supplied: Tablets, scored, pink, bottles of 50.

and in arthritis

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Each PARAFON WITH PREDNISOLONE tablet contains: PARAFLEX® Chlorzoxazone† 125 mg., TYLENOL® Acetaminophen 300 mg., and prednisolone 1.0 mg.

Dosage: One or two tablets t.i.d. or q.i.d.

Supplied: Tablets, scored, buff colored, bottles of 36.

Precautions: The precautions and contraindications that apply to all steroids should be kept in mind when prescribing PARAFON WITH PREDNISOLONE.

*sailor

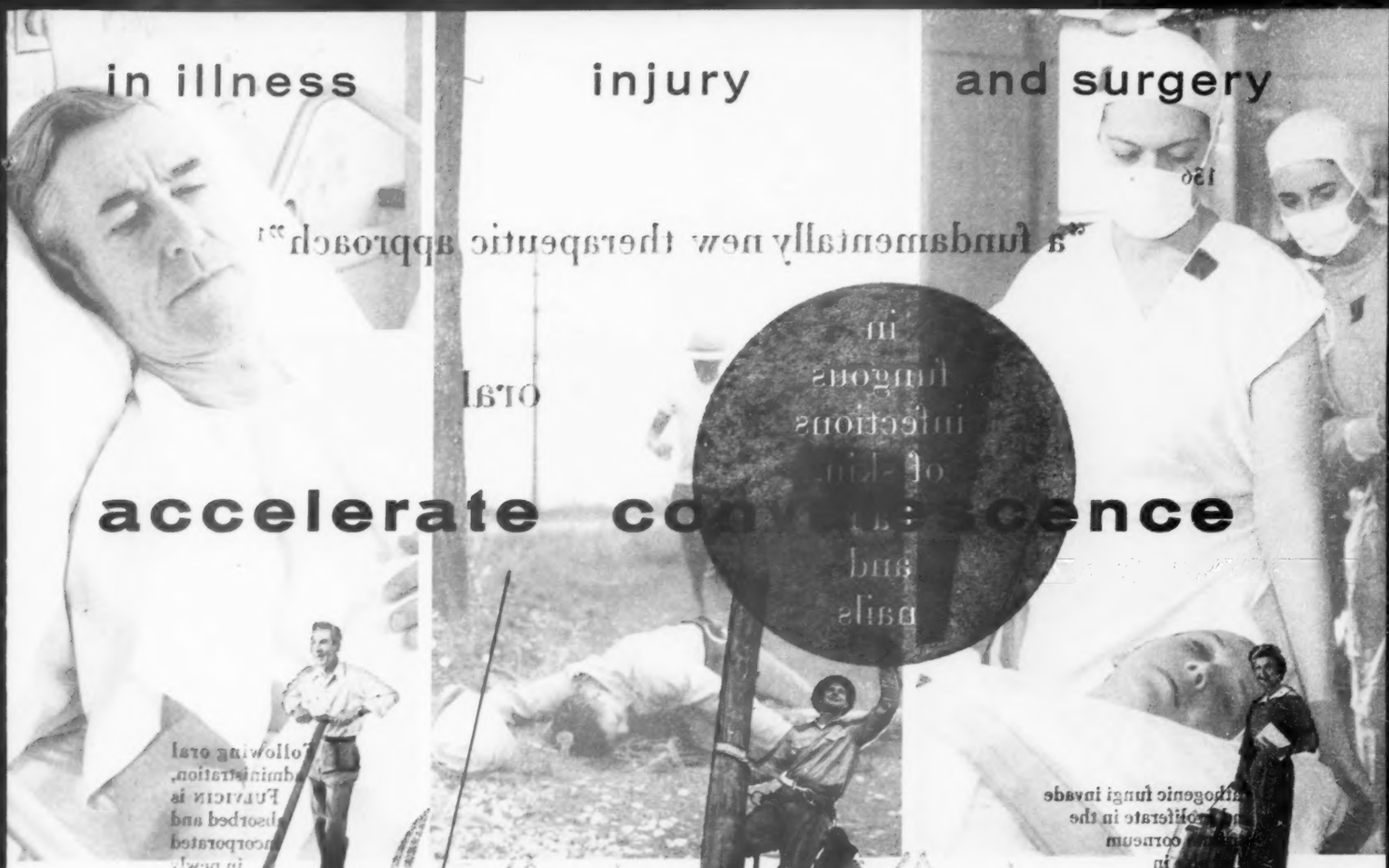
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1. Helbert, S. L.: Ann. New York Acad. Sc. 63: 147-164 (Oct. 28) 1955.

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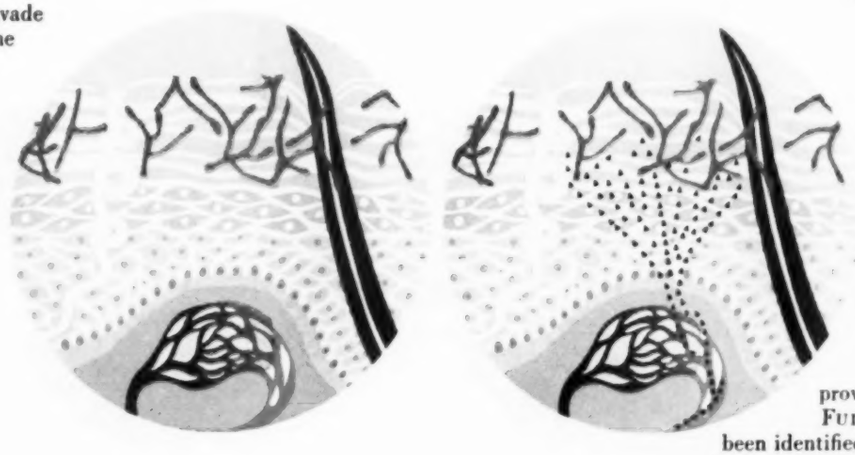
in fungous infections of skin, hair and nails

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FIRST EFFECTIVE PENETRATION OF KERATIN—FROM THE INSIDE

Pathogenic fungi invade and proliferate in the stratum corneum (and also in keratinized part of nails and hair), where they are usually inaccessible to treatment from the outside by topical antifungal agents, even with the aid of keratolytics.



Following oral administration, FULVICIN is absorbed and incorporated in newly growing dermal cells. As these cells approach the surface and become keratinized, they retain sufficient amounts of FULVICIN to provide fungistasis. FULVICIN has also been identified in hair shafts in fungistatic concentrations.[2]

"CURLING FACTOR" INHIBITS FUNGAL GROWTH —PERMITS OUTGROWTH OF HEALTHY TISSUE

Hyphal (filamental) tips of fungi are curled, contorted and stunted by FULVICIN.[3] Growth ceases, further penetration of keratin halts, and the fungal disease is arrested.



Fungus immobilized by FULVICIN is cast off as keratin grows out and sloughs off. Healthy tissue replaces infected keratin of skin, hair or nails.

Packaging: FULVICIN Tablets, 250 mg., bottles of 30, 100.

References: (1) Williams, D. I.; Marten, R. H., and Sarkany, I.: Lancet *2*:1212, 1958. (2) Gentles, J. C.; Barnes, M. J., and Fantes, K. H.: Nature *183*:256, 1959. (3) Brian, P. W.; Curtis, P. J., and Hemming, H. G.: Tr. Brit. Mycol. Soc. *29*:173, 1946.

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New...for the metabolic treatment of

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ANTURAN™

(sulfinpyrazone GEIGY)

High Potency Uricosuric Agent

By significantly increasing renal excretion of urate and thus lowering plasma uric acid, the new highly potent uricosuric agent ANTURAN strikes directly at the basic metabolic defect in gout.

Exceptionally high potency...4 to 6 times that of probenecid†...is the outstanding characteristic of ANTURAN. The effectiveness of ANTURAN is retained indefinitely and tolerance to it is good.

Clinically, ANTURAN:

- Prevents formation of new tophi
- Causes gradual absorption of old tophi
- Relieves chronic pain
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ANTURAN is not designed for the treatment of acute attacks for which BUTAZOLIDIN* is recommended. **Detailed Information On Request**

†Yü, T. F.; Burns, J. J., and Gutman, A. B. Arth. & Rheumat. 1:532, 1958.

ANTURAN™ (sulfinpyrazone GEIGY). Scored tablets of 100 mg. in bottles of 100.

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Decongestant / Antihistamine

THE POTENTIATED DECONGESTANT

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provides symptomatic relief of nasal congestion and rhinorrhea of allergic or infectious origin

Many patients whose symptoms are inadequately controlled by decongestants or antihistamines alone respond promptly and safely to 'ACTIFED'

'ACTIFED' contains:	in each tablet	in each tsp. Syrup
Triprolidine Hydrochloride	2.5 mg.	1.25 mg.
and Pseudoephedrine Hydrochloride	60 mg.	30 mg.

and effective for patients of all ages suffering from upper respiratory tract congestion

DOSAGE	TABLETS	SYRUP (5 cc. tsp.)
Adults and older children	2	2 tsp. every 4 hours
Children 4 months to 6 years of age through 3 months	½	½ tsp. every 4 hours

Original

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relieves painful muscle spasm, improves mobility, facilitates rehabilitation...

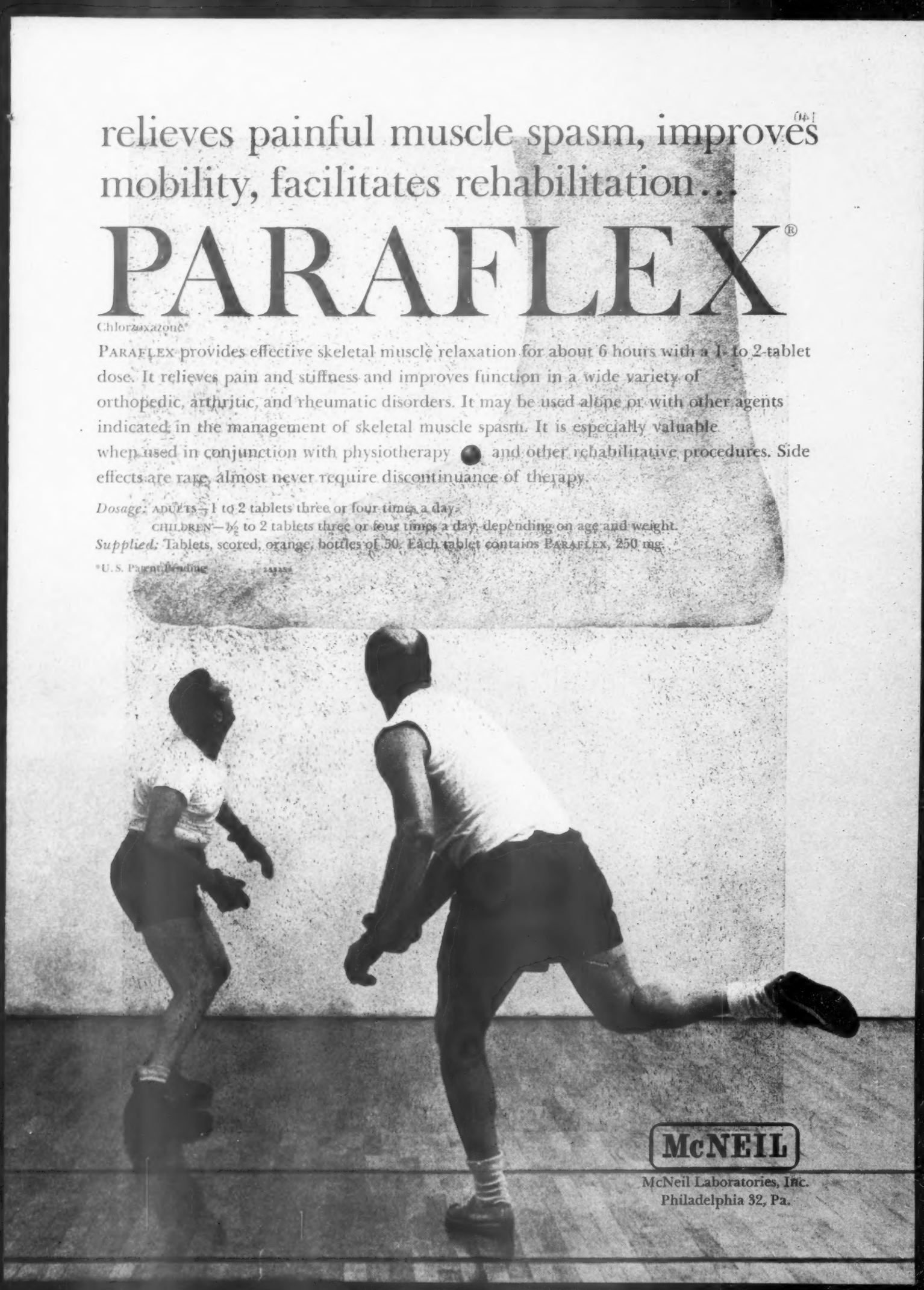
PARAFLEX®

Chlorzoxazone*

PARAFLEX provides effective skeletal muscle relaxation for about 6 hours with a 1- to 2-tablet dose. It relieves pain and stiffness and improves function in a wide variety of orthopedic, arthritic, and rheumatic disorders. It may be used alone or with other agents indicated in the management of skeletal muscle spasm. It is especially valuable when used in conjunction with physiotherapy and other rehabilitative procedures. Side effects are rare, almost never require discontinuance of therapy.

Dosage: ADULTS—1 to 2 tablets three or four times a day.
CHILDREN—½ to 2 tablets three or four times a day, depending on age and weight.
Supplied: Tablets, scored, orange, bottles of 50. Each tablet contains PARAFLEX, 250 mg.

*U.S. Patent Pending



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PROMOTES HEALING WITH STRIKING EFFECTIVENESS IN MOST DERMATOSES

STEROSAN-Hydrocortisone (Cream and Ointment) elicits prompt improvement in a wide variety of allergic and inflammatory skin disorders, yet is virtually non-irritating and non-sensitizing. Its striking effectiveness in promoting healing has been repeatedly stressed by independent investigators: "...a highly satisfactory formulation for ...dermatologic lesions having both pyogenic and allergic components."[1] "...a most useful medication in the treatment of chronic eczematoid and lichenified skin lesions."[2] "...valuable...for many eczematous dermatoses, for pyodermas, and for several pruriginous skin disorders."[3] "...was effective in treating various dermatoses in 82 per cent of 203 patients...."[4] STEROSAN®-Hydrocortisone (brand of chlorquinaldol with hydrocortisone) Cream and Ointment; each contain 3 per cent of STEROSAN and 1 per cent of hydrocortisone. In tubes of 5 Gm. and 20 Gm. Prescription only. Also available: STEROSAN® (brand of chlorquinaldol) 3 per cent Cream and Ointment. Tubes of 30 Gm. and jars of 1 lb. Prescription only. (1) Lubowe, I. I.: Antibiotic Med. & Clin. Therapy 4:81, 1957. (2) Pace, B. F.: M. Rec. & Ann. 51:370, 1957. (3) Murphy, J. C.: Rocky Mountain M. J. 55:53 (June) 1958. (4) Fox, H. H.: Antibiotic Med. & Clin. Therapy 6:85, 1959.

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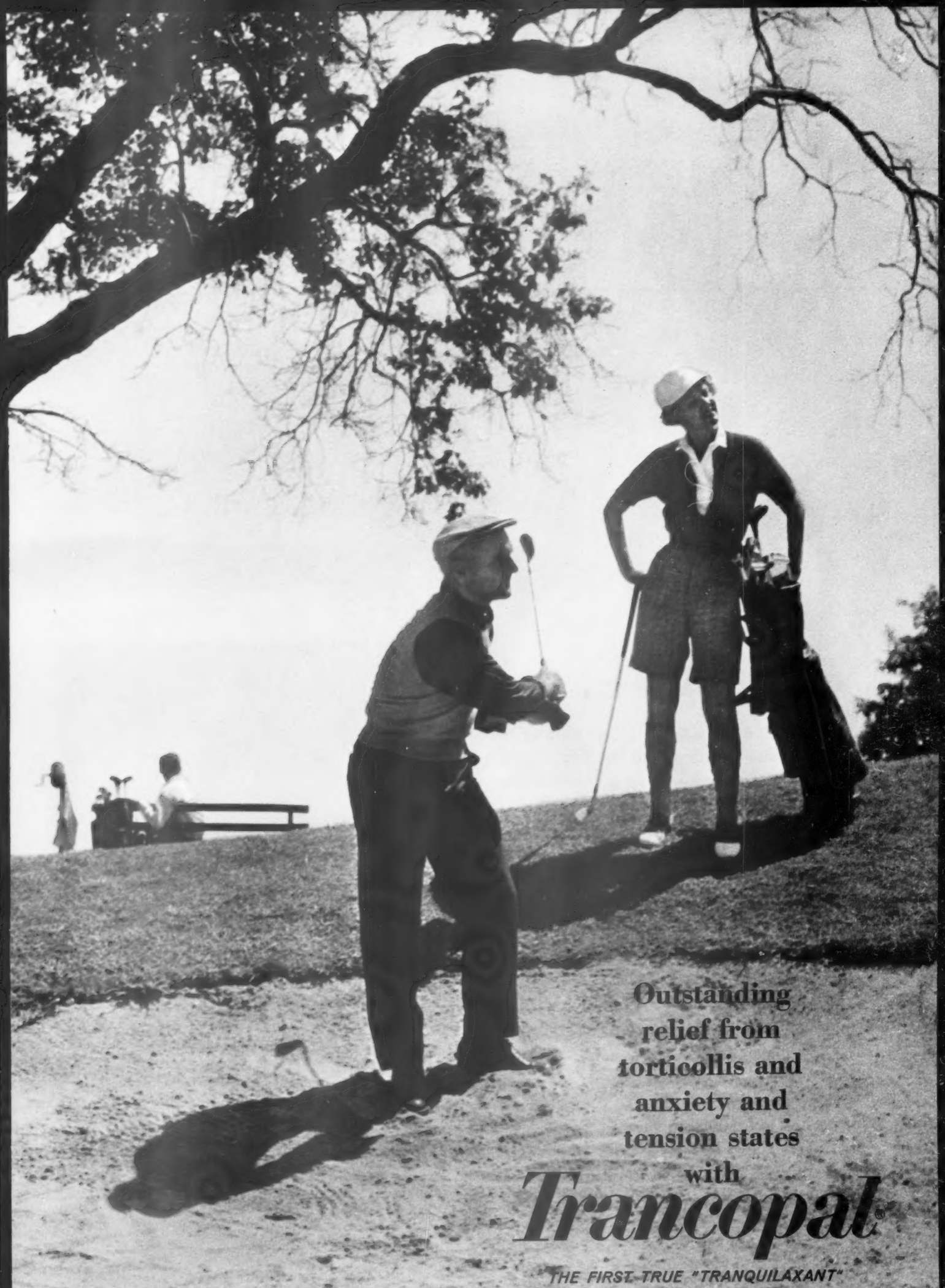
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Outstanding
relief from
torticollis and
anxiety and
tension states
with
Trancopal®
THE FIRST TRUE "TRANQUILAXANT"

Here is what you can expect when you prescribe

case profile no. 2840*

A 55-year-old man complained of a painful, very stiff neck on the left side. There was marked muscle spasm that seemed to involve primarily the trapezius muscle. He had a severe headache, with the pain radiating down the left side of the neck to the shoulder. There were no other findings on physical examination and results of routine laboratory tests were normal.

Trancopal was prescribed in a dosage of 200 mg. q.i.d. The first and second dose of Trancopal gave only moderate relief. However, after the third dose, there was marked relief of the stiffness of the neck, as well as the headache and shoulder pain.

After the fourth dose, medication was gradually decreased and was discontinued on the sixth day. One week later, the patient had moderate recurrence of the torticollis, and Trancopal was again prescribed in doses of 200 mg. q.i.d. The patient obtained complete relief in one day and no further treatment was required.

for torticollis



THE FIRST TRUE "TRANQUILAXANT"

Trancopal®

for anxiety and tension states



case profile no. 3382*

A 35-year-old woman, a professional model, had an acute, severe attack of anxiety. She was irrational and unable to eat, and was very restless.

Initial medication consisted of aspirin with codeine and later meprobamate. Neither was effective, and the patient's condition became worse. She had to be hospitalized because of the marked anxiety. Trancopal was then prescribed in a dosage of 200 mg. q.i.d., in addition to bed rest.

After the second dose of 200 mg. of Trancopal, the patient became calm and rational, and was able to eat. The dosage of Trancopal was gradually reduced to 100 mg. q.i.d. on the fourth hospital day, after which the patient was discharged and was able to return to her normal occupation.

**Clinical Reports on file at the Department of Medical Research, Winthrop Laboratories.*

Turn page for complete listings of Indications and Dosage.

THE FIRST TRUE "TRANQUILAXANT"

Trancopal

potent MUSCLE RELAXANT
effective TRANQUILIZER

Indications:

Musculoskeletal[1]	Psychogenic[1]
Neck pain (torticollis, etc.)	Anxiety and tension states
Low back pain (lumbago, etc.)	Dysmenorrhea
Bursitis	Premenstrual tension
Rheumatoid arthritis	Asthma
Osteoarthritis	Angina pectoris
Disc syndrome	Alcoholism
Fibrositis	
Ankle sprain, tennis elbow, etc.	
Myositis	
Postoperative muscle spasm	

Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in fifteen to thirty minutes and lasts from four to six hours. The higher dosage is recommended for the treatment of patients in the acute stages of painful musculospastic conditions, and anxiety and tension states. Children (5 to 12 yrs.), 50 mg. three or four times daily.

Supply:



Trancopal Caplets®

100 mg. (peach colored, scored), bottles of 100.

New strength ▶ 

Trancopal Caplets

200 mg. (green colored, scored), bottles of 100.

"Chlormethazanone [Trancopal] not only relieved painful muscle spasm, but allowed the patients to resume their normal activities with no interference in performance of either manual or intellectual tasks."[2]

"The effect of this preparation in these cases [skeletal muscle spasm] was excellent and prompt . . ."[3]

". . . Trancopal is a most valuable drug for relieving tension, apprehension and various psychogenic states."[4]

1. Collective Study, Department of Medical Research, Winthrop Laboratories.
2. Lichtman, A. L. (N.Y. Polyclinic M. Sch. & Hosp.): Kentucky Acad. Gen. Pract. J. 4:28, Oct., 1958.
3. Mullin, W. G., and Epifano, Leonard (Long Island College Hosp.): Am. Pract. & Digest Treat. To be published.
4. Ganz, S. E. (New York, N. Y.): J. Indiana M. A. 52:1134, July, 1959.

Winthrop LABORATORIES
New York 18, New York

Trancopal (brand of chlormezanone) and Caplets, trademarks reg. U.S. Pat. Off. Printed in U.S.A. 9-59 (1400M)



IN STRESS CONDITIONS SUCH AS:

- Spontaneous abortion
- Inflammatory diseases
- Infectious diseases
- Cardiovascular diseases
- Metabolic diseases

CAPILLARY AND VASCULAR DAMAGE ARE COMMON FINDINGS

In these stress conditions whether caused by nutritional deficiencies, environment, drugs, chemicals, toxins, virus or infections

HESPERIDIN, HESPERIDIN METHYL CHALCONE or LEMON BIOFLAVONOID COMPLEX

are indicated as therapeutic adjuncts for the control and management of the associated capillary and vascular damage.

Sunkist and Exchange Brand Hesperidin and Lemon Bioflavonoid Complex are available to the medical profession in specialty formulations developed by leading pharmaceutical manufacturers.

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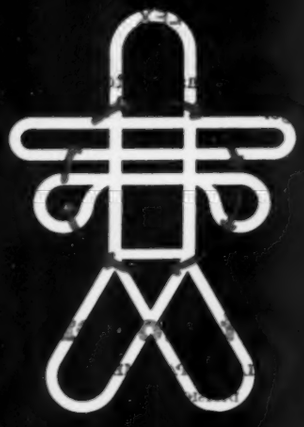
DISSOLVES INTRAVASCULAR

NOT JUST A NEW DRUG... *A NEW THERAPY*

ACTASE

TRADEMARK

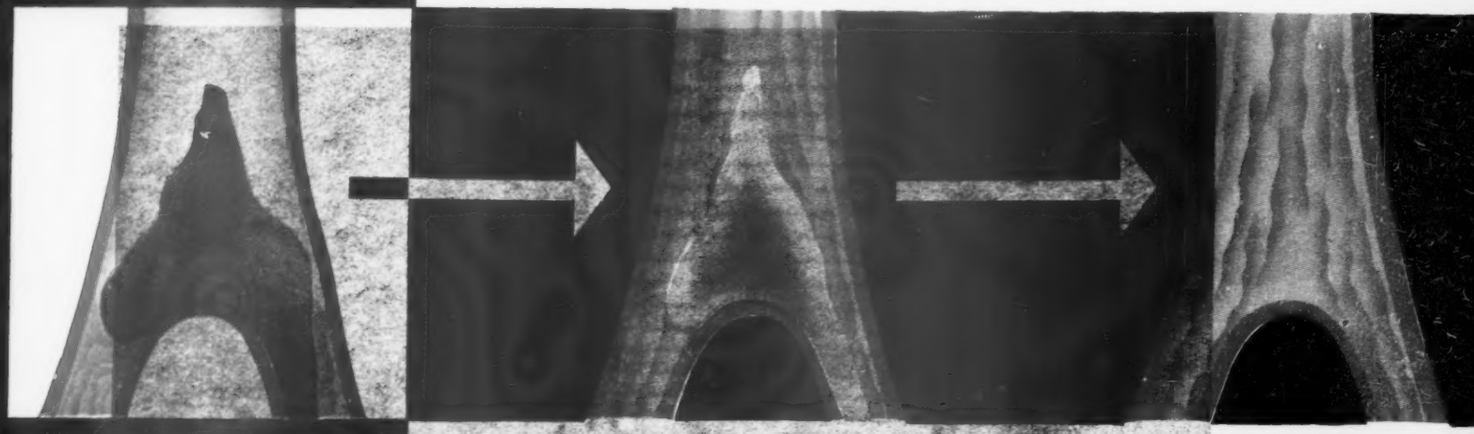
Fibrinolysin (Human)



1. Moser, K.M.: J.A.M.A. *167*:1695 (Aug. 2) 1958.
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3. Sussman, B.J., and Fitch, T.S.P.: J.A.M.A. *167*:1705 (Aug. 2) 1958.
4. Singher, H.O., and Chapple, R.V.: Clin. Med. *6*:439 (March) 1959.

ORTHO PHARMACEUTICAL CORPORATION, RARITAN, N. J.

CLOTS in thrombophlebitis and pulmonary embolism

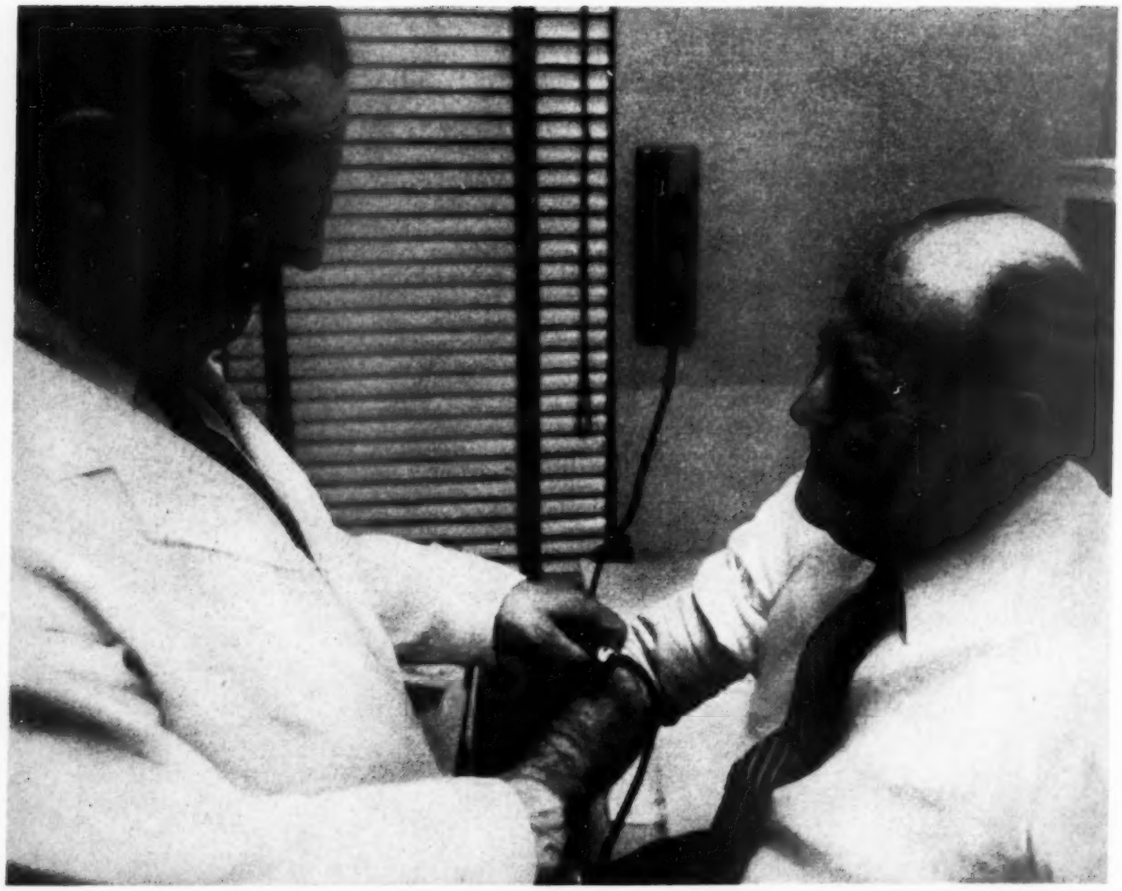


Clinically proved,[1-3] ACTASE has a specific lytic effect upon the venous thrombus or pulmonary embolus. Patients respond rapidly, often dramatically, to the clot-dissolving action of an intravenous infusion of this physiologic fibrinolysin.[4] A significant decrease in length of hospitalization following thrombophlebitis, as well as a reduction in the threat of pulmonary embolism, is now possible. In one series of patients with deep thrombophlebitis, some of whom had previously suffered pulmonary emboli, no occurrence of pulmonary emboli was reported following administration of ACTASE.[1]

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hypertensive
with or without
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FOR EXAMPLE: "A clinical study made of syrosingopine [Singoserp] therapy in 77 ambulant patients with essential hypertension demonstrated this agent to be effective in reducing hypertension, although the daily dosage required is higher than that of reserpine. Severe side-effects are infrequent, and this attribute of syrosingopine is its chief advantage over other Rauwolfia preparations. The drug appears useful in the management of patients with essential hypertension."[1]

Almost all side effects relieved when Singoserp was substituted for other rauwolfia derivatives in 24 patients[2]

Side Effects	Incidence with Prior Rauwolfia Agent	Relieved by Singoserp	Not Relieved*
Depression	11	10	1
Lethargy or fatigue	5	5	0
Nasal congestion	7	7	0
Gastrointestinal disturbances	2	0	2
Conjunctivitis	1	1	0

*Two of the 24 patients had two troublesome side effects.

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First drug to add in hypertensive patients already on medication

Supplied: Singoserp *Tablets*, 1 mg. (white, scored); bottles of 100. Samples available on request. Write to CIBA, Box 277, Summit, N. J.

1. Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. *169*:1609 (April 4) 1959.
2. Bartels, C. C. Clinical report to CIBA.

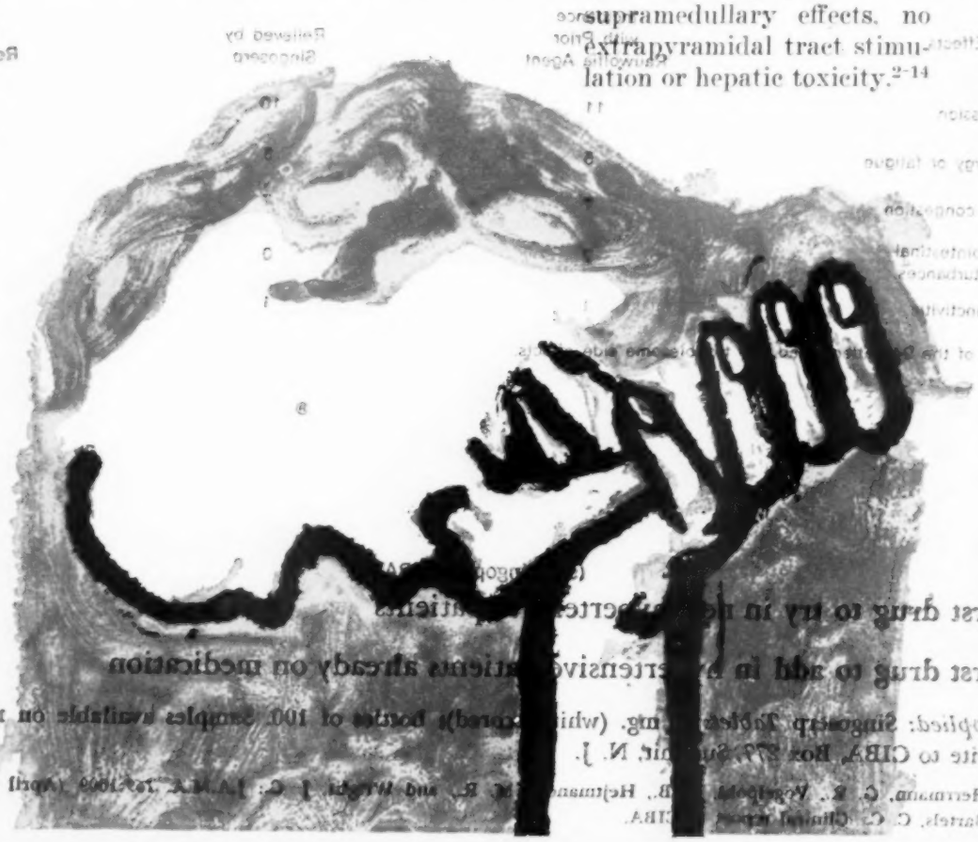
stop as well as prevent nausea and vomiting

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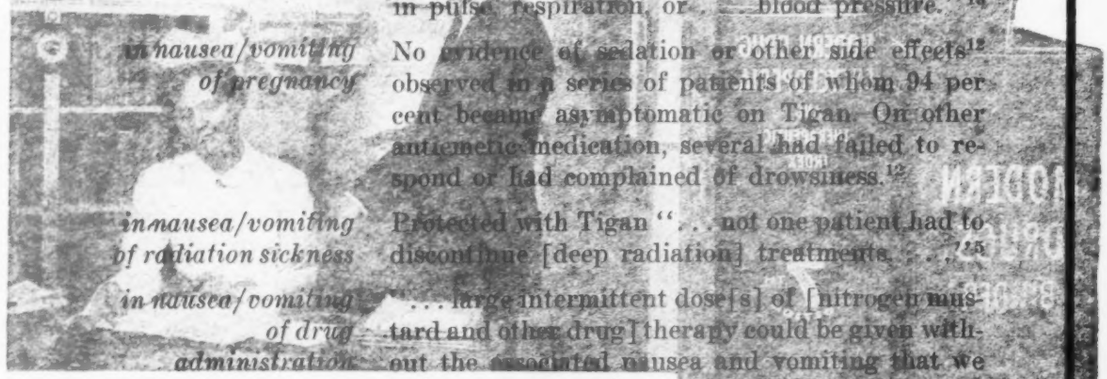
Tigan blocks emetic impulses at the chemoreceptor trigger zone (CTZ),[1] a medullary structure activating the vomiting center. While Tigan shares with the phenothiazines the mode of antiemetic action, this is their only similarity.[1] In extensive clinical studies[1-8] Tigan, unsurpassed in specificity, has exhibited a virtually complete absence of side effects. Tigan has demonstrated no sedative or tranquilizing properties, no hypotensive or supramedullary effects, no extrapyramidal tract stimulation or hepatic toxicity.[2-14]



no special precautions—
no known contraindications

in nausea/vomiting of gastrointestinal disorders

Complete or moderate relief in 78 per cent of acute or chronic gastroenteritis patients.[13] "We did not find a single toxic reaction . . . no side effects, such as sedation, skin rash . . . no changes in pulse, respiration, or . . . blood pressure."[13]



in nausea/vomiting of pregnancy

No evidence of sedation or other side effects[12] observed in a series of patients of whom 94 per cent became asymptomatic on Tigan. On other antiemetic medication, several had failed to respond or had complained of drowsiness.[12]

in nausea/vomiting of radiation sickness

Protected with Tigan "... not one patient had to discontinue [deep radiation] treatments. . . ."[15]

in nausea/vomiting of drug administration

"... large intermittent dose[s] of [nitrogen mustard and other drug] therapy could be given without the associated nausea and vomiting that we had seen before."[7]

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specific antiemetic antinauseant

no sedative properties
no tranquilizer side effects

Suggested uses: Both prophylactic and therapeutic control of nausea and vomiting associated with pregnancy, motion sickness, gastrointestinal disorders, operative procedures, carcinomatoses, toxicoses, other underlying disease processes, drug administration and radiation therapy.

Dosage: Adults — 1 or 2 capsules, orally; 2 cc intramuscularly, q.i.d. or 1 suppository, q.i.d. For children's dosage, consult literature.

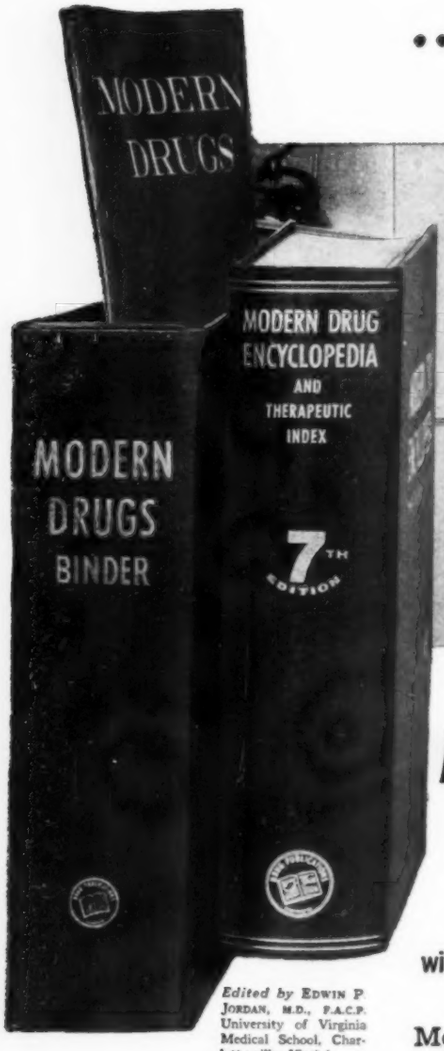
In nausea and vomiting of pregnancy — Satisfactory control is usually achieved with an initial dose of two capsules immediately upon awakening. If possible, the patient should remain in bed for one-half to one hour following this dose. When nausea and vomiting are not confined to the morning hours, supplemental doses of one or two capsules should be given throughout the day at intervals of three to four hours.

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References: 1. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap.*, in press. 2. W. F. Harris and R. Kaufman, L. Goldman and A. Bernstein, to be published. 3. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp.*, 9:189, 1958. 4. O. C. Brandman, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 5. J. A. Ludlam, *ibid.* 6. D. W. Molander, *ibid.* 7. J. C. Stanley, *ibid.* 8. W. S. Derrick, *ibid.* 9. B. Wolfson and F. F. Foldes, *ibid.* 10. L. McLaughlin, *ibid.* 11. Reports on file, Roche Laboratories. 12. 101 clinical communications. 13. W. K. Gauthier, Discussant at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 14. H. L. Davis, *ibid.*



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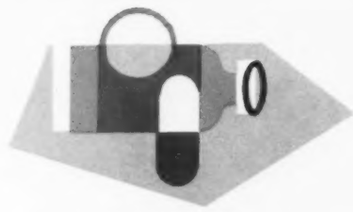
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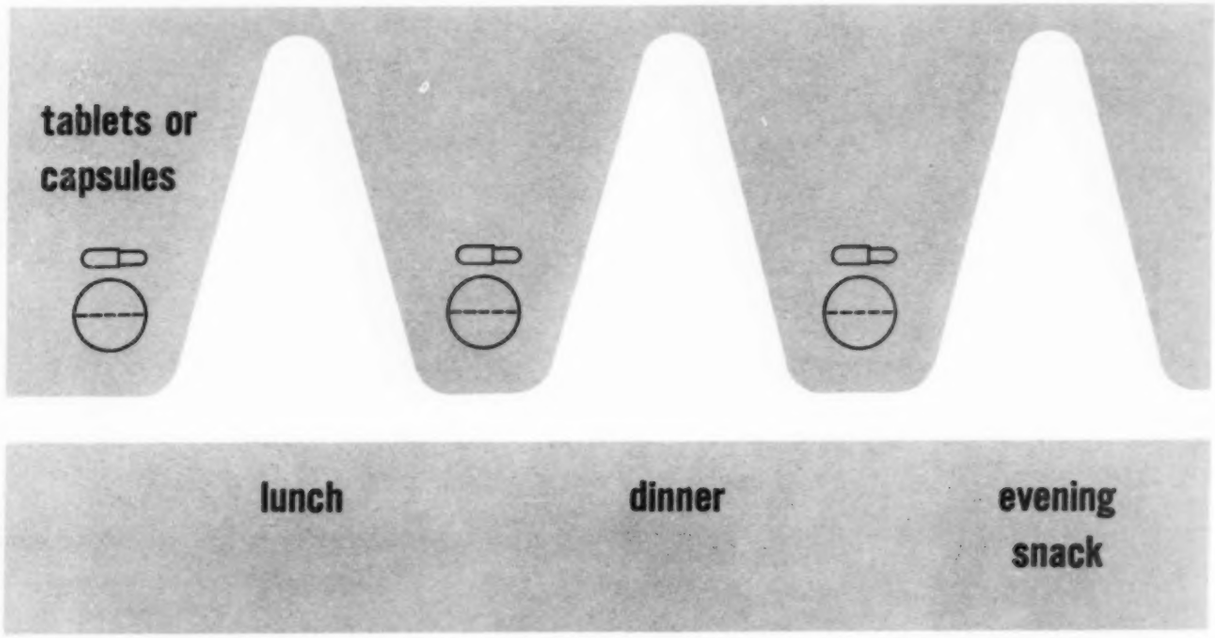
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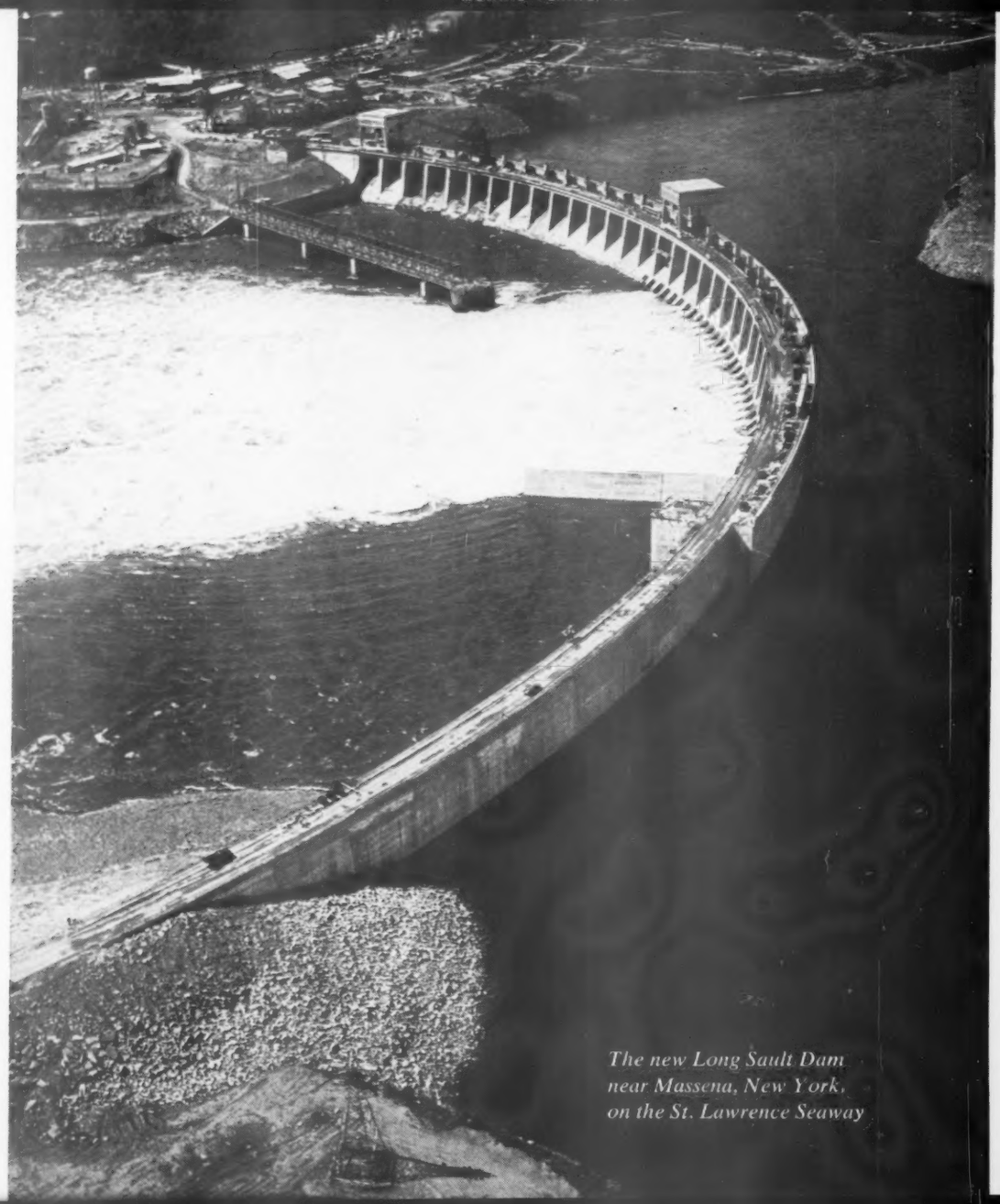
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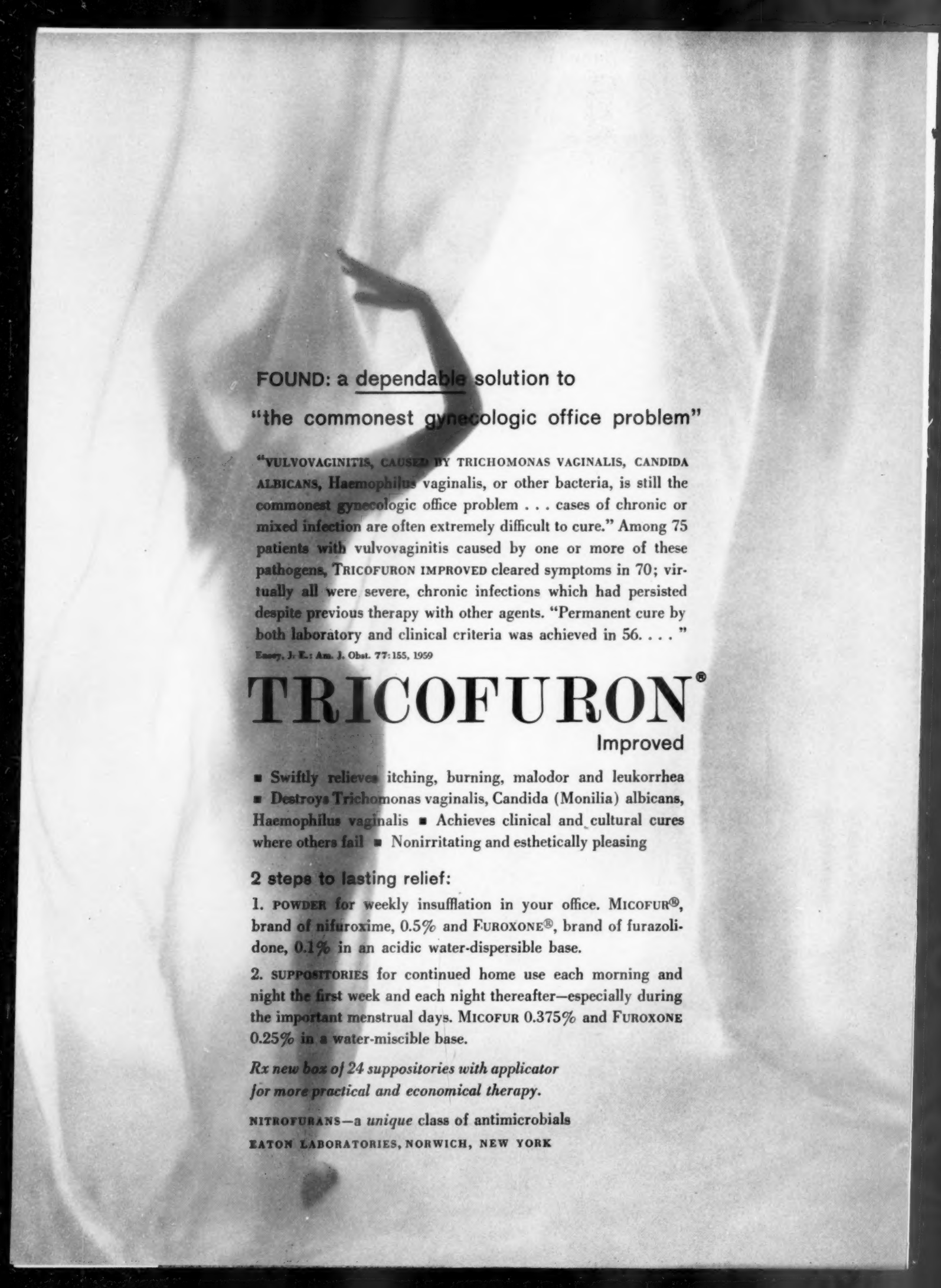
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Emery, J. L.: Am. J. Obst. 77:155, 1959

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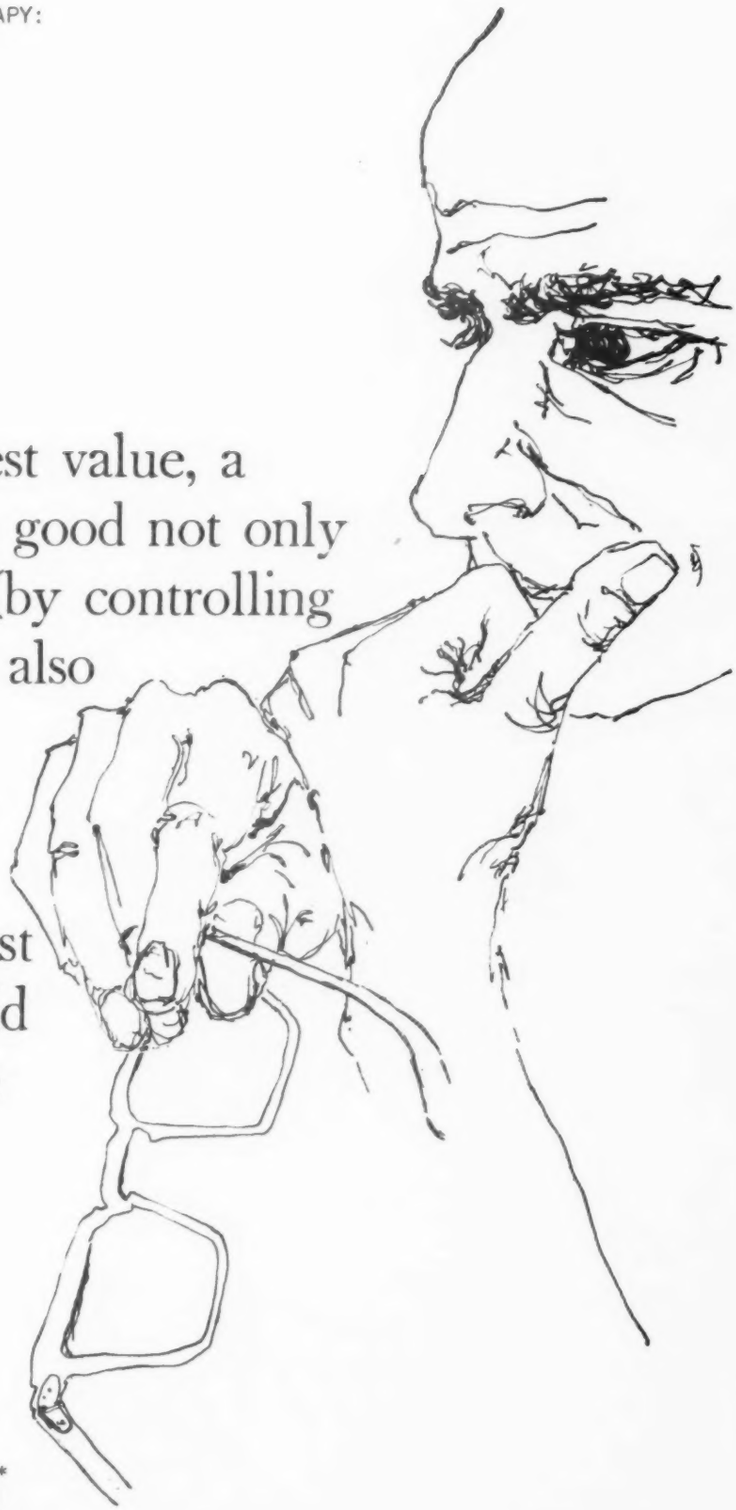
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1. Brock, S., Mod.: Bull. New York Acad. Med. 32:202, 1956.
2. Doshay, L. J.: Parkinsonism and Its Treatment. Philadelphia, J. B. Lippincott, 1954, pp. 87-88.
3. Doshay, L. J., Constable, K., and Zier, A.: Neurology 3:360, 1953.

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